A Phase I Clinical Trial of Thoracic Radiotherapy and Concurrent Celecoxib for Patients with Unfavorable Performance Status Inoperable/Unresectable Non–Small Cell Lung Cancer

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Abstract

Objectives: Preclinical observations that selective cyclooxygenase-2 inhibitors enhance in vitro cell radiosensitivity and in vivo tumor radioreponse led to clinical trials testing therapeutic efficacy of these agents. Our study was designed to determine whether the COX-2 inhibitor celecoxib could be safely administered in doses within those approved by the Food and Drug Administration when used concurrently with thoracic radiotherapy in patients with poor prognosis non–small cell lung cancer (NSCLC).

Patients and Methods: The trial consisted of three cohorts of patients: (a) locally advanced NSCLC with obstructive pneumonia, hemoptysis, and/or minimal metastatic disease treated with 45 Gy in 15 fractions; (b) medically inoperable early-stage NSCLC treated with definitive radiation of 66 Gy in 33 fractions; and (c) patients who received induction chemotherapy but who were not eligible for concurrent chemoradiotherapy trials. These patients received 63 Gy in 35 fractions. Celecoxib was administered p.o. on a daily basis 5 days before and throughout the course of radiotherapy. Celecoxib doses were escalated from 200, 400, 600, to 800 mg/d given in two equally divided doses. Two to eight patients of each cohort were assigned to each dose level of celecoxib.

Results: Forty-seven patients were enrolled in this protocol (19 in cohort I, 22 in cohort II, and 6 in cohort III). The main toxicities were grades 1 and 2 nausea and esophagitis, and they were independent of the dose of celecoxib or radiotherapy schedule. Only two patients in group II developed grade 3 pneumonitis 1 month after treatment, one on 200 mg, and the other on 400 mg celecoxib. Celecoxib-related toxicity developed in 3 of 47 patients: an uncontrolled hypertension in one patient on 800 mg celecoxib and hemorrhagic episodes in 2 patients (shoulder hematoma in one and hemoptysis in the other) on 200 mg celecoxib who were on warfarin for other medical reasons. Of 37 patients evaluable for tumor response, 14 had complete response, 13 partial responses, and 10 stable or progressive disease. The actuarial local progression-free survival was 66.0% at 1 year and 42.2% at 2 years following initiation of radiotherapy.

Conclusions: These results show that celecoxib can be safely administered concurrently with thoracic radiotherapy when given up to the highest Food and Drug Administration–approved dose of 800 mg/d, which we used. A maximal tolerated dose was not reached in this study. The treatment resulted in actuarial local progression-free survival of 66.0% at 1 year and 42.2% at 2 years, an encouraging outcome that warrants further assessment in a phase II/III trial.

Lung cancer is the second most common malignancy in man and a leading cause of cancer death in the United States (1). At the time of diagnosis, only a small percentage of patients (15-25%) present with early-stage non–small cell lung cancer (NSCLC) and these patients are usually treated with curative surgical resection. However, the majority of NSCLC patients present with locally advanced disease that cannot be cured by surgical removal of their tumors; consequently, combined chemotherapy and radiation therapy remains the preferred treatment for these patients. Chemotherapy given either sequentially or concurrently with radiation therapy increases the survival of these patients (2, 3), although the effect is, in general, modest and seen predominantly in patients with good prognostic factors (minimal weight loss <5%, Karnofsky performance status >70%). Improvements in therapeutic efficacy by the combined chemoradiotherapy have unfortunately
been achieved at the expense of increased acute normal tissue toxicity, such as esophagitis and pneumonitis, particularly when chemotherapeutic agents were administered during the course of radiation treatment.

It is apparent that further improvements in the treatment of lung cancer are needed. Targeting molecules and signaling pathways that are altered in cancer cells, resulting in dysregulated cell proliferation and suppression of cell death, is a therapy approach that is undergoing extensive preclinical and clinical investigations. Agents that selectively target altered molecules and signaling in cancer cells are not expected to influence normal tissues; hence, when these agents are combined with cytotoxic agents, no increase in normal tissue damage is anticipated. Our understanding of the biology of NSCLC has greatly increased in recent years, with evidence being acquired that diverse molecular processes that normally regulate growth, survival, and function of lung epithelial cells become dysregulated during the pathogenesis of NSCLC and result in aggressive tumor behavior (4, 5). One of those molecular changes consists of expression of cyclooxygenase-2 enzyme (COX-2) by tumor cells.

There are two isoforms of the COX enzyme, COX-1 and COX-2 (6). COX-1 is a ubiquitous enzyme, constitutively expressed in virtually all tissues and is responsible for production of prostaglandins, which regulate normal homeostatic physiologic functions. In contrast, COX-2 is absent from most normal tissues, but is induced by various factors, such as proinflammatory cytokines, mitogenic substances, oncogenes, and hypoxia, in inflamed tissues and tumors in which it mediates prostaglandin production (7). COX-2 is often overexpressed in premalignant lung lesions and established NSCLC (8, 9). Its presence in NSCLC has been linked to more aggressive tumor growth, facilitation of metastatic spread, and poor patient survival (9–11).

Increasing evidence shows that COX-2 or its products, prostaglandins, may be involved in tumor protection against damage by cytotoxic agents including radiation (12, 13). Treatment with selective COX-2 inhibitors has been shown to enhance in vitro cell radiosensitivity (14–16) and in vivo tumor response to radiation (17, 18), including human tumor xenografts derived from lung cancer (16). The enhancement of tumor radioresponse occurred without appreciable increase in radiation-induced normal tissue injury, indicating that COX-2 inhibitors are able to increase the therapeutic ratio of radiotherapy (17, 18). The mechanisms of enhancement of tumor radioresponse by COX-2 inhibitors seem to be multiple, involving both direct actions on tumor cell radio sensitivity (14, 16, 19) and indirect actions via inhibition of tumor neoangiogenesis (15, 17, 18). COX-2 inhibitors have also been reported to potentiate tumor response to chemotherapeutic agents (20–22).

The preclinical findings that suggest COX-2 inhibitors have potential to improve radiotherapy or chemoradiotherapy have stimulated assessment of the therapeutic efficacy of these agents in clinical trials. Here we describe the results of a phase I clinical trial at the University of Texas M. D. Anderson Cancer Center that combined the selective COX-2 inhibitor celecoxib with radiotherapy for patients with poor prognosis NSCLC.

Patients and Methods

Study design and patient selection. This clinical trial was reviewed and approved by our institutional review board. The primary objective of the study was to determine whether the COX-2 inhibitor celecoxib could be safely administered in doses within those approved by the Food and Drug Administration when used concurrently with thoracic radiotherapy in patients with poor prognosis NSCLC. The patients included those who were not candidates for chemotherapy treatment or chemoradiation protocols at our institution and those who received induction chemotherapy and referred for consolidative thoracic radiation. The secondary objective was to evaluate tumor response to this treatment regimen.

There were three cohorts of patients in this study. Cohort I comprised of patients who needed palliative thoracic radiation to relieve the local-regional symptoms caused by tumor mass. These patients presented with stage III to IV (one site of metastatic disease outside of the thorax) and obstructive pneumonia, or hemoptysis, and had poor Karnofsky performance status (<70%; weight loss >5%). Cohort II included patients needing definitive thoracic radiation therapy for their stage I or II NSCLC. These patients had medical comorbidities, such as poor pulmonary function, cardiac disease, or other conditions that rendered them medically not suitable for surgery. Cohort III included patients with locally advanced stage IIIA/B NSCLC whose induction chemoradiotherapy was initiated before they were referred to our institution, and thoracic radiation was indicated for consolidation. These patients were usually not candidates for other prospective protocols in our institution.

Pretreatment evaluations. Pretreatment evaluations included medical history, physical examination, and laboratory and radiographic studies. Records were made of Karnofsky performance status, weight loss, and history of use of COX-2 inhibitors, gastric ulcer, gastrointestinal bleeding, and renal or hepatic disease. Laboratory studies included complete blood counts (CBC) with differential, platelet count, SMA-12, electrolytes, liver functional tests, and urinalysis. Radiographic tests included chest X-rays, computerized tomography scans of chest (including upper abdomen), brain image, and radionuclide bone scan. Positron emission tomography (PET) was done when clinically indicated. All patients had pulmonary functional tests before treatment. All patients had a biopsy of the tumor. If the biopsy was done before patients came to our institution, stained and unstained slides or tissue blocks were requested from the diagnosing hospital and pathologic diagnosis was confirmed by a pathologist in our institution.

Treatments. Thoracic radiotherapy was delivered utilizing megavoltage photons. Patients in cohort I received palliative radiation to a total dose of 45 Gy at 3 Gy/fraction daily in 3 weeks. Patients in cohort II received definitive radiation therapy to a total dose of 66 Gy at 2 Gy/fraction daily in 6.5 weeks. Patients in cohort III received total radiation dose of 63 Gy at 1.8 Gy/fraction daily in 7 weeks after induction chemotherapy, the latter completed in an outside institution before patient’s referral to our institution. Gross target volume included complete extent of visible primary tumor and lymph nodes as defined radiographically. Clinical target volume was 8 mm from the gross target volume, and planning target volume was minimum of 7 mm or a maximum of 13 mm from the clinical target volume. Supraclavicular lymph nodes and lymph nodes in the contralateral hilum were not routinely included in the radiation field. Three-dimensional treatment planning was used, and radiation doses were prescribed to an isodose line covering 95% of the planning target volume with lung heterogeneity correction. Radiation beam energy was defined by the optimized treatment plan.

Celecoxib, at doses of 200 to 800 mg, was administered p.o. starting 5 to 7 days before the first fraction of radiotherapy and continued throughout the course of radiotherapy. The doses of celecoxib were escalated from 200, 400, 600, to 800 mg/d given in two equally divided doses. Patients were required to fill a pill diary to assess the compliance of celecoxib treatment. The treatment schema and dose levels of celecoxib are summarized in Table 1.

Follow-up, toxicity criteria, and tumor response. Informed consents were obtained on all patients before registration. Patients were assessed weekly during radiation therapy, 4 to 6 weeks after completion of radiation therapy, and every 3 months thereafter. Patient history,
physical examination, laboratory tests, and chest X-ray tests as described above were done at each visit. Computerized tomography scan of the chest to assess the status of the tumor was done at 4 to 6 weeks after completion of radiotherapy and every 6 months thereafter.

The Radiation Therapy Oncology Group Acute Radiation Morbidity Scoring Criteria (23) was used to assess the adverse effect of this treatment regimen and the patient data management system was used for data collection. All toxic effects encountered during the study were evaluated according to the grading system (0-4). Any life-threatening and/or unexpected and serious (grade 3 or 4) toxic effects were reported immediately to the study chairperson who, in turn, would notify the surveillance committee.

Tumor response to the treatment was evaluated using computerized tomography scan of the chest. Complete response was defined as disappearance of clinical evidence of the treated tumor lasting for a minimum of 4 weeks. Partial response was defined as ≥50% decrease in the sum of the products of diameters of a measured lesion lasting for a minimum of 4 weeks. No response was defined as any regression of the tumor less than partial response. Progressive disease was defined as any increase of ≥25% in the sum of the products of diameters of treated lesion at any time after completion of the treatment. Local progression-free survival (LPFS) was defined as the duration from the date of diagnosis to the date of the first evidence of progression or recurrence in the irradiated local-regional tumor. Overall survival was defined as the duration from the date of diagnosis to the date of death.

Statistical considerations. The continuous reassessment method was used to determine the maximum tolerated dose of celecoxib for each of the three treatment groups was used (24). The dose-limiting acute toxicities defined in this study was any grade 3 or greater acute toxicities, including radiation esophagitis or pneumonitis, which usually ranged from 5% to 10% with radiation only at our institution. The objective and the particular stopping rules were the doses of celecoxib that produced any grade 3 or greater acute toxicity rate as close to 35% as possible or the highest dose level of 800 mg celecoxib per day was reached. In addition, toxicities clearly unrelated to radiation but more likely related to celecoxib only (such as hypertension, coagulation problem, acute myocardia infarction, etc.) are observed and recorded. The model used was the exponential with a normal prior distribution with mean 0 and SD 1.34 (i.e., choice 1 of the continuous reassessment method program). Cohorts of two patients were entered at each dose level. No escalation of dose was done until the toxicity outcome of all patients at the next lower dose is known. The trial was stopped when a dose-limiting toxicity was observed at any celecoxib dose level or eight to nine patients on each cohort received the highest dose of 800 mg celecoxib without toxicity.

Results

Patient characteristics are summarized in Table 2. Forty-seven patients were enrolled in this protocol (19 in cohort I, 22 in cohort II, and 6 in cohort III). There were 27 female and 20 male patients. The median age of patients was 65 years (range 49-87 years). There were 7 stage IA, 9 stage IB, 1 stage IIA, 6 stage IIB, 2 stage IIIA, 7 stage IIIB, and 15 stage IV patients. There were 14 patients on 200 mg, 7 on 400 mg, 8 on 600 mg, and 18 on 800 mg celecoxib dose levels. No patients were enrolled on 600 and 800 mg celecoxib dose levels for cohort III because of a change in standard practice during the time of this trial that concurrent chemoradiation became a more acceptable therapy for this population.

Of the 47 patients, 2 were not evaluable for toxicity related to this treatment modality, and all were in cohort I (one patient started with radiotherapy on the emergent basis before initiation of celecoxib and the other patient had a change in treatment plan). In all three cohorts, grade 1 and 2 fatigue were the main toxicity observed (28 of 45, 62.2%), followed by grade 1 and 2 esophagitis (23 of 45, 51%), grade 1 and 2 skin erythema (17 of 45, 37.7%), and grade 1 nausea (1 of 45). Pneumonitis occurred in 10 of 45 (22.2%); two were categorized as grade 3. One of the two patients who had long-standing chronic obstructive pulmonary disease and oxygen dependence who required increased oxygen supplement 1 month after completion of radiation and celecoxib treatment. The other patient had history of malignancy treated with chemotherapy and radiation, who developed bilateral pneumonitis, had evidence of pulmonary embolism on spiral computerized tomography, and superimposed radiation pneumonitis, and eventually died of hemorrhage to the air space of the lung secondary to her pulmonary embolism. In both cases, radiation pneumonitis developed 1 month after radiotherapy was completed and 1 month after celecoxib administration was discontinued. These toxicities were independent of the doses of celecoxib or radiotherapy schedules.

Celecoxib-related toxicity developed in three patients in cohort II. One patient, who was on anticoagulant therapy for a cardiovascular disease prior and during celecoxib 400 mg/d plus radiotherapy treatment, developed pruritic papular rash, coagulation abnormalities (increased prothrombin time = 37.0, partial thromboplastin time = 56.3, and international normalized ratio = 8.66), and a shoulder hematoma after 27 days of celecoxib administration. Further treatment with celecoxib was discontinued. Another patient in the same celecoxib dose level presented with hemoptysis and was diagnosed with a stage IIIB NSCLC. At the time, the patient

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<table>
<thead>
<tr>
<th>Table 1. Treatment schema</th>
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<tbody>
<tr>
<td><strong>Week 1</strong></td>
</tr>
<tr>
<td>Celecoxib</td>
</tr>
<tr>
<td>Cohort I*</td>
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<tr>
<td>Cohort II</td>
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<tr>
<td>Cohort III</td>
</tr>
</tbody>
</table>

*Patients in cohort I took celecoxib for a total of 4 weeks.

NOTE: Celecoxib (c) was started 5 to 7 days before radiation start. The dose levels were as follows: level 1, 200 mg/d, 100 mg p.o. twice a day; level 2, 400 mg/d, 200 mg p.o. twice a day; level 3, 600 mg/d, 300 mg p.o. twice a day; level 4, 800 mg/d, 400 mg p.o. twice a day. The doses of radiation therapy (x) were as follows: cohort I, 45 Gy/15 fractions at 3 Gy/fraction daily; cohort II, 66 Gy/33 fractions at 2 Gy/fraction daily; cohort III, 63 Gy/35 fractions at 1.8 Gy/fraction daily.

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was on warfarin therapy for a cardiovascular disease. After one dose of celecoxib administration, the patient had a mild hemoptysis and further administration of celecoxib was discontinued. A bronchoscopic examination of this patient showed no active bleeding. The third patient at 800 mg celecoxib per day developed hypertension after she has received 21 of 33 fractions of radiation therapy at 2 Gy/fraction. It was felt that the hypertension was due to celecoxib and the drug was discontinued. However, her blood pressure did not return to normal after the discontinuation of celecoxib during the treatment, and only normalized after she finished the whole course of the radiation. These three patients were included in toxicity evaluation but not in tumor response evaluation (Table 3).

There were 41 patients who finished the whole course of assigned treatments (excluding two patients who never started celecoxib treatment, three who developed celecoxib related toxicity, and one additional patient in cohort I who did not finish celecoxib therapy because of his refusal). Tumor response was not evaluable in four patients (one with pleural effusion that prevented any accurate measurement of tumor; three failed to return for follow-up). Of the remaining 37 patients, 14 had complete response, 13 partial response, and 10 had no response or disease progressions by radiographic evaluation. The overall major response rate was 65.8% (Table 4). The 12-month actuarial LPFS rates were 65.0% for the entire group, 34.2% for cohort 1, 74.2% for cohort 2, and 100% for cohort 3, respectively (Figs. 1 and 2). There was no difference in toxicity, tumor response, or rates of LPFS among three cohorts of patients or different dose levels of celecoxib. The actuarial 2-year overall survival rates were 54.6% for the entire group, 20.9%, 66.9%, and 75% for cohort I, II and III, respectively.

**Discussion**

The rationale of the current study was that inhibiting COX-2 activity might enhance tumor response to radiation therapy without increasing the risk of treatment related toxicities. It was based on preclinical research showing that treatment with selective COX-2 inhibitors strongly enhanced radioresponse of both rodent tumors (17, 18) and human tumor xenografts in nude mice (16, 19) without significant

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**Table 2. Pretreatment characteristics and response (number of patients)**

<table>
<thead>
<tr>
<th>Characteristics (total = 47)</th>
<th>Cohort 1 (n = 19)</th>
<th>Cohort 2 (n = 22)</th>
<th>Cohort 3 (n = 6)*</th>
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<tbody>
<tr>
<td>Median age (range)</td>
<td>68 (49-86)</td>
<td>74.5 (53-88)</td>
<td>64 (43-64)</td>
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<tr>
<td>Sex (female:male)</td>
<td>8:11</td>
<td>14:8</td>
<td>5:1</td>
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<tr>
<td>Stage</td>
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</tr>
<tr>
<td>IA/B</td>
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<tr>
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<td></td>
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<tr>
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<tr>
<td>IV</td>
<td></td>
<td>12</td>
<td>3</td>
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<tr>
<td>Celecoxib dose level (mg)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>4</td>
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<tr>
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<td>3</td>
<td>2</td>
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<tr>
<td>600</td>
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<td>4</td>
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<tr>
<td>800</td>
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*This cohort was closed to accrual after six patients owing to a change of practice based on the evidence that concurrent chemoradiation was more effective than sequential chemoradiation, resulting in slow accrual for this cohort.

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**Table 3. Toxicity**

<table>
<thead>
<tr>
<th>Celecoxib dose (mg)</th>
<th>Esophagitis (grade)</th>
<th>Skin (grade)</th>
<th>Fatigue (grade)</th>
<th>Pneumonitis (grade)</th>
<th>Other (grade)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>Cohort 1 (n = 19), thoracic irradiation 45 Gy/25 fractions once daily</td>
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<tr>
<td>200</td>
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<td>800</td>
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<td>3</td>
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<tr>
<td>Cohort 2 (n = 22), thoracic irradiation 66 Gy/33 fractions once daily</td>
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<td>200</td>
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<td>6</td>
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<td>4</td>
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<tr>
<td>Cohort 3 (n = 6), thoracic irradiation 63 Gy/35 fractions once daily</td>
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<td>800</td>
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*Patients on anticoagulating therapy. One had hemoptysis after 1 dose of celecoxib; the other had hematoma of the shoulder after 2 weeks of celecoxib.

*Patient developed hypertension during treatment. The hypertension did not normalize after discontinuation of celecoxib.
modification of radiation damage of normal tissues. The normal tissues investigated include mouse jejunum (18), tissues whose damage results in leg contractures (18), and lung (25).

The data of our present study showed that celecoxib could be safely administered in doses within those approved by the Food and Drug Administration up to 800 mg/d when used concurrently with thoracic radiotherapy in patients with poor prognosis NSCLC. For example, no clinically significant (grade 3) acute esophagitis was observed in this study to require narcotic pain medication during radiation. Two patients that developed grade 3 pneumonitis had either underlying or superimposed pulmonary conditions that complicated both the diagnosis and management of this lung toxicity, and it is uncertain whether these toxicities could be attributed to celecoxib treatment. We realized that, in our study, it was difficult to separate the toxicity from radiation and drug therapy, especially with regard to radiation-induced pneumonitis due to the fact that high proportion of the population included in this study had chronic obstructive pulmonary disease, cardiac conditions, and poor performance status.

The advantage in using selective COX-2 inhibitors compared with standard nonsteroidal anti-inflammatory drugs is their lower toxicity, particularly that of the gastrointestinal tract, such as bleeding and ulcers (26). However, there are concerns that selective COX-2 inhibitors may be prothrombotic and increase the risk of myocardial infarction as shown in a study that compared selective COX-2 inhibitors with nonsteroidal anti-inflammatory drugs that showed a significantly higher risk of myocardial infarction in patients receiving rofecoxib versus naproxen (27). The results of a similar study of celecoxib versus ibuprofen or diclofenac (28) showed no increased risk for myocardial infarction attributable to celecoxib. No patients on our study had any cardiac event, but two patients developed hemorrhagic events that could be attributed to celecoxib treatment. However, both patients were on anticoagulant treatments for other medical conditions before and during the trial. These hemorrhagic events necessitated discontinuation of celecoxib and, subsequently, patients taking anticoagulants were not enrolled on the protocol. The dose of celecoxib in this study ranged between 200 and 800 mg daily, the doses approved by the Food and Drug Administration, and because of low toxicity observed in the study no maximum tolerated dose could be determined.

There has been a number of phase I or phase II clinical trials, either completed or still ongoing, exploring the use of selective COX-2 inhibitors in combination with other treatments for NSCLC, almost exclusively with chemotherapy (Table 5). Most trials used celecoxib at a dose of 400 mg given twice a day and showed no dose-limited toxicity. A few trials reported some hematologic toxicity (29–34). Recently, Altorki et al. (35) completed a phase II trial using celecoxib in combination with carboplatin and paclitaxel as neoadjuvant therapy in patients with resectable stage IB to IIIA NSCLC, where celecoxib was given daily (400 mg twice a day) during chemotherapy. Twenty-nine patients were enrolled of whom 26 completed preoperative celecoxib treatment. The major toxicity was grade 3 or 4 neutropenia observed in 18 patients (62%), and the authors considered that addition of celecoxib was well tolerated. The overall clinical response rate was 65% that included 17% complete response and 48% partial response, which was concluded to be the improvement compared with chemotherapy alone. Importantly, the authors assessed the levels of prostaglandin E2 (PGE2) in the primary tumors and adjacent normal lung tissue, and found that tumor PGE2 levels were increased after chemotherapy only but this increase was abrogated by addition of celecoxib. However, no change in PGE2 levels in normal lung tissue was observed by these treatments. Thus, this study is the first of clinical trials that provided.

<table>
<thead>
<tr>
<th>Cohorts</th>
<th>CR</th>
<th>PR</th>
<th>NR/PD</th>
<th>Inevaluable</th>
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<tr>
<td>1 (n = 15)</td>
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<td>7</td>
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<td>2 (n = 20)</td>
<td>9</td>
<td>6</td>
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<tr>
<td>3 (n = 6)</td>
<td>3</td>
<td>2</td>
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<tr>
<td>Total (N = 41; %)</td>
<td>14 (34.1)</td>
<td>13 (31.7)</td>
<td>10 (24.4)</td>
<td>4 (9.8)</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; PR, partial response; NR, no response; PD, progressive disease.
proof of principle that the administration of celecoxib at 800 mg/d is sufficient to lower the intratumoral COX-2–derived PGE2 biosynthesis in patients with NSCLC, suggesting the need for measuring tumor levels of PGE2 to monitor biological effects of selective COX-2 inhibitors.

With respect to the mechanisms of potentiation of antitumor efficacy of radiation or chemotherapeutic drugs by selective COX-2 inhibitors, they are multiple and include both direct action on tumor cells and indirect actions through mainly inhibition of tumor neovascularization and stimulation of antitumor immune rejection responses (36–38). Selective COX-2 inhibitors may act by inhibiting COX-2–mediated pathways that results in inhibition of prostaglandin production, or via COX-2–independent mechanisms that include inhibition of nuclear factor-kB, inhibition of activating protein 1, alteration of the mitogen-activated protein kinase cascade, and activation of signal transducer and activator of transcription-1 among others (39). COX-2–independent mechanisms usually prevail when a large dose of COX-2 inhibitors is used, and these mechanisms can also result in antitumor actions against tumors not expressing COX-2 (40). Inhibition of PGE2 production in tumors is an important mechanism of antitumor efficacy of selective COX-2 inhibitors on their own and when combined with radiation or chemotherapy. Zweifel et al. (41) reported that treatment of tumor-bearing animals with anti-PGE2 antibody was effective in inhibiting tumor growth similarly to celecoxib. PGE2 and some other prostaglandins act as radioprotective substances (42), and their inhibition was

| Table 5. Summary of clinical trials using Celecoxib in combination with other treatments for NSCLC |
|-----------------------------------------------|-------------|---------------|-----------|-----------------|-----------------|
| Author                                      | Study design | Celecoxib     | CTX       | RT              | Toxicity     | Tumor response |
| Liao et al., current study                   | Phase I     | Dose escalation 100-400 mg bid | I. None | I. 45 Gy/15 fx | No dose-limiting toxicity | CR = 34.1% |
|                                              |             |               |           | II. None       |                | PR = 31.7%    |
|                                              |             |               |           | III. None      |                | RR/PD = 24.4% |
|                                              |             |               |           | III. None      |                | ORR = 65%     |
|                                              |             |               |           | III. None      |                | CR = 17%      |
|                                              |             |               |           | III. None      |                | PR = 48%      |
| Altorki et al., 2003 (35)                    | Phase II preoperative | 400 mg bid | Carboplatin and paclitaxel | None | No unexpected chemotherapy-related toxicity | ORR = 24% |
|                                              |             |               |           | Gemcitabine/ carboplatin up to eight cycles | No dose-limiting toxicity at ≥500 mg bid | SD = 56% |
|                                              |             |               |           | Weekly paclitaxel |              | PD = 20%      |
| Burton et al., 2004 (29)                     | Phase II elderly | 400 mg bid | Docetaxel up to 61 cycles | None | No dose-limiting toxicity | ORR = 23% |
|                                              |             |               |           | None           |                | PR = 10%      |
|                                              |             |               |           | None           |                | TTP = 10 wk   |
| Shehadeh et al., 2003 (30)                   | Phase II   | 400 mg bid | Docetaxel every 3 wk | None | No dose-limiting toxicity | PR = 4.5% |
|                                              |             |               |           | None           |                | SD = 82%      |
|                                              |             |               |           | None           |                | TTP = 19.6 wk |
| Gadgeel et al., 2003 (31)                    | Platinum refractory | 400 mg bid | Docetaxel | None | No dose-limiting toxicity | CR = 2.3% |
|                                              | Phase II Relapsed/ refractory |               | every 3 wk | None |                | PR = 23.3% |
|                                              |             |               |           | None           |                | SD = 42%      |
|                                              |             |               |           | None           |                | TTP = 13 wk   |
| Nugent et al., 2003 (32)                     | Phase II     | Paclitaxel weekly | None | No dose-limiting toxicity | CR = 2.3% |
|                                              |               |               |           |               |                | PR = 23.3% |
|                                              |               |               |           |               |                | SD = 42%      |
|                                              |               |               |           |               |                | TTP = 13 wk   |
| Kersztes et al., 2004 (34)                   | 2 × 2 Randomized second line | 400 mg bid | Irinotecan/ gemcitabine or irinotecan/ docetaxel | None | May have increased hematologic toxicity | Did not enhance efficacy |

Abbreviations: CTX, chemotherapy; RT, radiation therapy; fx, fraction; bid, twice daily; ORR, overall response rate; SD, stable disease; TTP, time to progression; OS, overall survival.
shown to result in the enhancement of tumor radio(chemo)response (41).

In conclusion, the results of our study show that celecoxib can be safely administered concurrently with thoracic radiotherapy when given up to the highest Food and Drug Administration–approved dose of 800 mg/d used here. A maximal tolerated dose was not reached in this study. The treatment resulted in actuarial LPSF of 66.0% at 1 year and 42.2% at 2 years, which is an encouraging outcome that warrants further assessment in a phase II/III trial.

References

A Phase I Clinical Trial of Thoracic Radiotherapy and Concurrent Celecoxib for Patients with Unfavorable Performance Status Inoperable/Unresectable Non–Small Cell Lung Cancer

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