Abstract

**Objectives:** Recent evidence has shown that cyclooxygenase-2 (COX-2) inhibitors have potent antitumor activity in prostate cancer both *in vitro* and *in vivo*. However, human trials are absent. This study evaluated the efficacy of the COX-2 inhibitor celecoxib in prostate-specific antigen (PSA) recurrent prostate cancer after radiation therapy (X-ray therapy or XRT) or radical prostatectomy.

**Methods:** Forty patients who had biochemical relapse after XRT or radical prostatectomy were treated with celecoxib 400 mg twice per day. Follow-up PSA levels were obtained at 3, 6, 12, and 18 months and subsequently every 6 months thereafter. Data were evaluated by calculating PSA doubling times and by calculating the slope of the curve of log(PSA) versus time to assess rate of PSA increase before and after celecoxib treatment for each patient.

**Results:** Thirty-six of 40 (90%) patients had a slowing effect on their rate of PSA after 3 months, including 11 of 40 with a decline and 8 of 40 with stabilization of PSA. Short-term responses at 3 months continued at 6, 12, 18 months. Comparison of rate of PSA increase before versus after celecoxib treatment showed significant flattening of slope of log(PSA) versus time from pretreatment for each of the time points. There was no significant change in testosterone levels, suggesting an androgen-independent mechanism.

**Conclusions:** COX-2 inhibitors may have an effect on serum PSA levels in patients with biochemical progression after XRT or radical prostatectomy. These results suggest that COX-2 inhibitors may help delay or prevent disease progression in these patients and thereby help extend the time until androgen deprivation therapy.

Cyclooxygenase-2 (COX-2) is an inducible gene that catalyzes the synthesis of prostaglandins from arachidonic acid. Aberrant or increased expression of COX-2 has been implicated in the pathogenesis of many diseases, including carcinogenesis. Increased expression of COX-2 is seen in association with decreased apoptosis, increased tumor invasiveness, immunosuppression, and angiogenesis (1–8). Furthermore, increased COX-2 expression correlates with poor differentiation, increased tumor size, increased nodal and distant disease, and decreased overall survival in a variety of cancers (7, 9–11). The precise *in vivo* mechanisms for COX-2 affect on tumor growth have not been determined but may include influences on tumor angiogenesis or immune-mediated growth (1–8).

COX-2 inhibitors have been shown to have antitumor activities in human colon, breast, lung, and prostate cancer tissues. Epidemiologic and clinical data regarding the potential antitumor effects of COX-2 inhibitors have been best described for colon cancer, suggesting both a therapeutic and chemopreventive role (10, 12–14). More recent studies have shown that COX-2 inhibitors may have a role in prostate cancer as well. COX-2 expression is increased in prostate cancer tissue, with consistently high levels observed in lymph node metastasis, suggesting that in the prostate, COX-2 may act early in tumor promotion and progression (15, 16). In prostate cancer cell lines, COX-2 is expressed in both androgen-responsive (LNCaP) and androgen-resistant (PC-3) cell lines, and exposure to COX-2 inhibitors results in the induction of apoptosis (17, 18). Some investigators have suggested that apoptosis occurs via down-regulation of bcl-2 (in LNCaP cell lines), whereas others have suggested a bcl-2-independent mechanism involving Akt inactivation in prostate cancer cell lines, including PC-3 (17, 18). More recently, *in vivo* studies on nude mice models injected with PC-3 cells have clearly shown that selective COX-2 inhibition has a dramatic antitumor effect, resulting in a >10-fold reduction in tumor surface area (93% reduction). This effect occurred via a combination of induction of tumor cell apoptosis and a down-regulation of tumor vascular endothelial growth factor (4).
Whereas the precise mechanism remains under investigation, the clinical potential of nonsteroidal anti-inflammatory drugs and COX-2 inhibitors, in particular, as an antitumor medication in prostate cancer is promising. Selective COX-2 inhibitors are easily available, with oral medications first earning Food and Drug Administration approval in 1998. The ability of such medications to selectively inhibit COX-2 (versus traditional nonsteroidal anti-inflammatory medications that provide both COX-1 and COX-2 inhibition) allows for the specific anti-inflammatory benefits without the associated toxicity (gastrointestinal, renal, and bleeding), which is derived from COX-1 inhibition. Recently, concerns of cardiovascular toxicity has limited the indiscriminate use of such medications especially with regard to first-line anti-inflammatory medication and has raised the concern about their use as a chemopreventive agent (19–22).

This study served as a phase II investigation to determine if COX-2 is indeed a potentially useful biological target by evaluating the efficacy of the COX-2-specific inhibitor celecoxib in prostate-specific antigen (PSA) recurrent prostate cancer after definitive radiation therapy or radical prostatectomy.

**Materials and Methods**

This study was done after review and approval by the Institutional Review Board of the University of North Carolina at Chapel Hill and was under surveillance by the Data Safety Monitoring Committee of the Lineberger Comprehensive Cancer Center at the University of North Carolina at Chapel Hill and in accordance with an assurance filed with and approved by the Department of Health and Human Services. The study was an investigator-initiated, industry sponsored (Pfizer, Inc., New York, NY) study.

Patients included into this study included those who had prior treatment with definitive radiation (at least 6,600 cGy, \( n = 32 \)) or radical prostatectomy (\( n = 8 \)) for clinically localized disease (clinical stage \( pT3 \) or \( pT4 \)). Table 1 shows the clinical and pathologic characteristics of the study cohort. All patients had shown evidence of biochemical failure within 5 years after definitive treatment: (a) detectable and increasing PSA after surgery (at least two values above the residual cancer detection limit of the assay), or (b) at least two increasing values above 1 ng/mL or at least three increasing values at any level after radiation therapy. Patients may have received neoadjuvant hormonal therapy but not in excess of 6 months and not within 6 months of entry into the study. Men who have undergone salvage radiation therapy after surgery and who have further evidence of biochemical progression (\( n = 16 \)) were included. Patients may have been on dietary treatments for prostate cancer but were not on any nonsteroidal anti-inflammatory medications except for a daily aspirin (dose not to exceed 325 mg/d).

Patients with clinical or radiographic evidence of metastatic disease were excluded from this study. In addition, patients who have received any adjuvant treatment (chemotherapy, hormonal therapy > 6 months) after definitive surgery or radiation therapy, with the exception of salvage radiation therapy after surgery and the exception of neoadjuvant hormonal therapy (as described above), were excluded from the study. Patients with a contraindication or allergy to COX-2 inhibitors were also excluded.

Forty patients who have had evidence of biochemical relapse after definitive radiation therapy or surgery were enrolled in this study. These patients were treated with celecoxib (Celebrex, Pfizer) 400 mg twice per day in an open label, nonblinded fashion. Follow-up PSA levels to assess efficacy were obtained at 3, 6, and 12 months after initiation of treatment. Serum testosterone levels were also obtained in 31 patients to confirm an androgen-independent mechanism of COX-2 effect. Patients were allowed to continue on therapy until (a) they exhibited evidence of PSA progression (as defined by three successive increases in their PSA with an absolute increase of at least 5 ng/mL above their baseline), or (b) they had clinical or radiographic evidence of distant metastases. After such progression, patients were removed from the trial.

PSA outcome was evaluated in two ways: (a) how the response changes over time [i.e., slope of line log(PSA) versus time [days]] before treatment versus after 3 months of treatment versus after 6 months of treatment versus after 12 months of treatment and, (b) as a change on the calculated PSA doubling time before treatment versus after 3 months of treatment versus after 6 months of treatment versus after 12 months of treatment versus after 18 months of treatment. PSA doubling time was calculated using the following formula: PSA doubling time = \( \log(2) \times t / \log(\text{final PSA}) - \log(\text{initial PSA}) \) (23). Post-therapy PSA doubling times and slopes [log(PSA) versus time] were compared with pretreatment values for each patient in a descriptive fashion categorizing patients by high (<6 months), moderate (6-12 months), or slow (>12 months) PSA doubling time, or as a stable/declining absolute value before and after treatment.

**Statistical methods.** In this study, we used the nonparametric Jonckheere-Terpstra method to test for ordered differences among categories. With this test, the null hypothesis is that the distribution of the response does not differ across ordered categories. We used the nonparametric Wilcoxon signed rank test on calculated paired difference scores and the sets of log(PSA) difference scores. All \( P \)s reported have been adjusted using the Bonferroni method to account for multiple testing or comparisons. Statistical analyses were done with SAS statistical software, version 8.2 (SAS Institute, Inc., Cary, NC; ref. 24).

**Results**

We examined PSA doubling time over the time points by categorizing the 40 patients the following way: high (<6 months), moderate (6-12 months), or slow (>12 months) PSA doubling time, or as a stable/declining absolute value before and after treatment. Table 2 shows the observed counts for each category. We noted that there was a significant shifting from the high and moderate to slow or stable/decline categories, which was highly significant at 3 months (\( P = 0.001 \), 6 months

Table 1. Clinical and pathologic characteristics of the study cohort

<table>
<thead>
<tr>
<th>Primary therapy</th>
<th>32</th>
<th>Radiation therapy</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y (range)</td>
<td>66 (55-82)</td>
<td>Gleason sum (%)</td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>12 (30)</td>
<td>7</td>
<td>20 (50)</td>
</tr>
<tr>
<td>8-10</td>
<td>8 (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathologic stage</td>
<td></td>
<td>pT2</td>
<td>13 (41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pT3</td>
<td>19 (59)</td>
</tr>
<tr>
<td>Mean primary/original PSA, ng/mL (range)</td>
<td>11.8 (1.3-51.2)</td>
<td>Mean prestudy PSA, ng/mL (range)</td>
<td>2.7 (0.6-7.5)</td>
</tr>
</tbody>
</table>

NOTE: Primary/original PSA is defined as PSA value before original definitive therapy. Prestudy PSA is defined as PSA value at the start of celecoxib therapy. Pathologic staging information is from the 32 patients who underwent radical prostatectomy.
At 3 months after initiating treatment, 36 of 40 (90%) patients had a slowing effect on their rate of PSA increase: 11 of 40 had a decline and 8 of 40 had stabilization of PSA. Of the remaining 21 patients, 17 had slowing of their PSA doubling time; mean increase (i.e., slowing) in PSA doubling time of 4.5-fold from pretreatment. Only 4 patients had no initial change in PSA doubling time at 3 months; yet, 3 of 4 eventually showed increase of PSA doubling time at all time points. Figure 1 shows the actual log(PSA) slopes at each time point connected by the median values. This figure reveals a persistent effect out to 18 months of follow-up. Figure 2 shows two patient examples, including a patient with high-risk disease who achieved a temporary slowing of his PSA doubling time (Fig. 2A) and a patient with a more typical course after initiation of celecoxib therapy (Fig. 2B). Due to the relatively small sample size, no correlations could be observed between response to treatment versus clinical variables, such as initial therapy modality (i.e., surgery versus radiation), stage, or grade of disease.

With regard to measurements of serum testosterone levels, there were no significant changes in pretreatment versus posttreatment levels of serum testosterone levels in 31 patients evaluated at both 3 and 6 months, suggesting an androgen-independent mechanism.

One patient experienced transient right-hand weakness while on study requiring hospitalization. Diagnostic radiologic studies were not conclusive, the patient was discharged with the diagnosis of a presumed TIA, and he was taken off of the study. No other cardiovascular toxicities or other serious adverse events were encountered.

### Discussion

Despite improved cure rates with definitive therapy for clinically localized prostate cancer, it is estimated that 25% to 50% of patients will develop biochemical relapse (i.e., a detectable and increasing serum PSA level) after surgery or radiation therapy (25–27). Such patients, who exhibit biochemical recurrence and have yet to show clinical signs of relapse, now represent a substantial and growing population of prostate cancer patients.

Currently, there are no clear, effective treatment options for patients with increasing PSA levels after definitive radiation therapy or surgery. The use of chemotherapy in prostate cancer has been uniformly disappointing in both a primary or adjuvant role (28). The lack of efficacy, combined with the toxicity of treatment, has rendered investigational the use of chemotherapy in this setting. Furthermore, potential benefits early hormonal (i.e., androgen ablation) therapy in these

### Table 2. PSA doubling times of the 40 patients categorized by high, moderate, or slow PSA doubling time, or as a stable/declining absolute value before and after treatment

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>High (&lt;6 mo)</th>
<th>Moderate (6-12 mo)</th>
<th>Slow (&gt;12 mo)</th>
<th>Stable/declining</th>
<th>Progressed/withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>19/40 (48%)</td>
<td>13/40 (33%)</td>
<td>8/40 (20%)</td>
<td>0/40 (0%)</td>
<td>0</td>
</tr>
<tr>
<td>3 mo</td>
<td>4/40 (10%)</td>
<td>4/40 (10%)</td>
<td>13/40 (33%)</td>
<td>19/40 (48%)</td>
<td>0</td>
</tr>
<tr>
<td>6 mo</td>
<td>2/40 (5%)</td>
<td>9/40 (23%)</td>
<td>18/40 (40%)</td>
<td>13/40 (33%)</td>
<td>0</td>
</tr>
<tr>
<td>12 mo</td>
<td>1/35 (3%)</td>
<td>7/35 (20%)</td>
<td>22/35 (63%)</td>
<td>5/35 (14%)</td>
<td>2</td>
</tr>
<tr>
<td>18 mo</td>
<td>0/17 (0%)</td>
<td>2/17 (12%)</td>
<td>14/17 (82%)</td>
<td>1/17 (6%)</td>
<td>3</td>
</tr>
</tbody>
</table>

NOTE: Significant shifting observed from high and moderate to slow or stable/decline categories at 3 months (P = 0.001), 6 months (P = 0.022), 12 months (P = 0.029), and 18 months (P = 0.040).

### Table 3. Mean and median slope of the log(PSA) versus time (×0.001) curves for the study patients, categorized by before therapy versus 3 months versus 6 months versus 12 months versus 18 months

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Mean slope</th>
<th>Median slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>1.57</td>
<td>1.8</td>
</tr>
<tr>
<td>3 mo</td>
<td>0.16</td>
<td>0</td>
</tr>
<tr>
<td>6 mo</td>
<td>0.45</td>
<td>0.5</td>
</tr>
<tr>
<td>12 mo</td>
<td>0.37</td>
<td>0.4</td>
</tr>
<tr>
<td>18 mo</td>
<td>0.34</td>
<td>0.4</td>
</tr>
</tbody>
</table>

NOTE: Statistically significant at 3 months (P = 0.001), 6 months (P = 0.0005), 12 months (P = 0.0005), and 18 months (P = 0.001).
patients are controversial and have not been shown to conclusively affect disease progression, survival, or quality of life and may unnecessarily expose patients to the side effects of hormonal therapy who are otherwise asymptomatic (28). Currently, a large number of these patients are simply watched expectantly until they develop clinically symptomatic or widely metastatic disease at which time hormonal therapy is instituted. Therapeutic alternatives, which are simple, relatively nontoxic, and efficacious, clearly need to be identified. COX-2 inhibitors may represent such an alternative for these patients.

In this phase II study, the COX-2 inhibitor celecoxib was used to treat patients with PSA recurrent prostate cancer after definitive radiation therapy or surgery. The goal of such treatment is to help delay or prevent disease progression in these patients and thereby extend the time until androgen deprivation therapy. Such a “broken arrow” effect, by extending the time between biochemical recurrence and clinical recurrence, may thereby help to preserve the quality of life in these patients. In addition, a slowing of the PSA increase may also have some effect on patient survival as well.

Our results suggest that an inhibitory affect on the logarithmic increase in PSA may occur with treatment with celecoxib, at least in the short term. Thirty-six of 40 patients (90%) had a significant inhibitory effect on their serum PSA levels after 3 months of treatment. In fact, 11 of these patients (28%) had an actual decline in their absolute PSA value, and an additional 8 (20%) had stabilization of their PSA level. Of the four patients who did not show initial slowing of their PSA doubling time, three eventually showed increase of PSA doubling time (2- to 4-fold) by 12 months of follow-up. Furthermore, the short-term responses at 3 months continued at 6, 12, and even 18 months of treatment as well. Similarly, comparison of the slope of log(PSA) versus time showed a significant flattening of the rate of PSA increase. Table 1 shows the effect of celecoxib on PSA increase in more clinically relevant terms: there seems to be a significant shift of patients with rapid doubling times towards slower doubling times or even stable/declining PSA values after treatment with celecoxib. Again, such results suggest an inhibitory affect on PSA increase with treatment.

This phase II trial represents the first report of the clinical use of COX-2 inhibitors in the treatment of prostate cancer. We had originally published a small pilot study of 12 patients with limited follow-up in the past that showed an inhibitory affect of celecoxib on PSA increase at a shorter-term follow-up (6 months). This trial confirms the findings of that original pilot investigation. However, the results showed in this phase II study should be interpreted with caution for several reasons. First, this study represents a limited sample size. Although all patients in this study had biochemically progressive disease before treatment, it is conceivable that some degree of PSA variability (either physiologic or intra-assay) may affect interpretation of the drug effect, and that this influence may be magnified with relatively small patient numbers.

Second, one must consider the potential of a placebo effect in treated patients. In a recent placebo-controlled trial of rosiglitazone in PSA-recurrent prostate cancer, Smith et al. observed that 40% of patients on placebo had increase in their PSA doubling time by >150% of baseline at a short-term follow-up. However, in this trial with short-term end points, such a “placebo effect” could likely be attributed to PSA variability and not drug (or placebo) effect. Longer PSA

![Individual Changes in the slope of the log PSA Rise](image1)

Fig. 1. Plot of slope of log(PSA) versus time (\(t<0.001\)) curves at pretreatment, 3, 6, 12, and 18 months of celecoxib. Time points significantly different from baseline \((P<0.001)\) by nonparametric ANOVA.

![Patient # 1 Gleason 4+5 pT3b](image2)

A

![Patient # 2 Gleason 4+3 pT2b](image3)

B

Fig. 2. Plot slope of PSA versus time for two patient examples including (a) a high-risk patient with pT3b, Gleason 4 + 4 disease with a pretreatment PSA doubling time of 2 months (A) and (b) a moderate-risk patient with pT2b, Gleason 4+3 disease with a pretreatment PSA doubling time of 12 months (B).
follow-up, as employed in the present study, would likely limit the random effects of PSA variability that can affect results in the short term. In addition, by using more broad categories of PSA doubling time (i.e., \(<6 \text{ versus } 6-12 \text{ versus } >\) 12 months versus stable/decline) the potential of “false-positive” results due to the arbitrary and more narrow definition of “positive outcome,” such as an increase in PSA doubling time of 150%, is minimized. (For example, an increase from 2 months to 3 months, considered a positive result in the rosiglitazone study, could readily be explained by PSA variability and may not signify a real effect on tumor growth.) Lastly, the use of PSA slope as an outcome measure may be superior to arbitrary categorization of positive outcomes or changes in PSA doubling time. In the trial of Smith et al., the authors note that PSA slope did not significantly change from baseline in the placebo group (slope decreased by 5.4% in the placebo group and by 33.6% in the rosiglitazone group). In fact, the authors seem to acknowledge the superiority of PSA slope as an outcome measure (versus their definition) in the discussion: “The mean posttreatment PSA slope did not change significantly from baseline in the placebo group, suggesting that a higher than expected rate of positive PSA doubling time outcomes was not due to temporal changes in tumor growth rate.” In the present study, PSA slope decreased by 78%, suggesting a potential effect on tumor growth rate. Nevertheless, the rosiglitazone trial points out the potential for such PSA variability or a “placebo effect” in a nonrandomized, noncontrolled study and emphasizes the importance in carefully choosing outcome measures in both noncontrolled and controlled studies.

Third, follow-up is relatively short, especially with regard to the natural history of PSA recurrent disease. True beneficial effects of such a medication would potentially come from long-term treatment and efficacy to thereby delay time to progression of clinically symptomatic disease. Fourth, the extrapolation of short-term PSA effects to long-term clinical outcome should always be undertaken with caution. Although PSA levels have been correlated to disease burden and PSA doubling times correlated to disease progression and the development of metastatic disease, the ability of a treatment to affect such PSA end points does not necessarily constitute long-term beneficial clinical response. Thus, one should not overstate the beneficial antitumor effects of celecoxib based on this study alone.

Lastly, the recent findings of the potential cardiovascular risks of selective COX-2 inhibitor must be taken into account when considering the clinical use of these medications. The NIH has recently suspended a large national colon adenoma prevention with celecoxib (Adenoma Prevention with Celecoxib) trial due to findings at 3 years of an increased risk of cardiovascular events for participants taking the 400 mg daily and 800 mg daily dose of the drug (2.5% and 3.4%, respectively) compared with placebo (1.0% refs. 20, 29). The differences in cardiovascular safety became apparent only after several years, emphasizing the importance of long-term follow-up needed to address drug safety. (Of note, Pfizer reports in a second chemoprevention trial, the Prevention of Spontaneous Adenomatous Polyps trial, that there was no greater cardiovascular risks than placebo; ref. 29). These findings are being evaluated in the context of the trials and other large body of data that exist and that has been accumulated over time in arthritis patients at high doses in which serious cardiovascular events have not been seen. Still, the long-term use of COX-2 inhibitors, especially at high doses, may increase ones cardiovascular risk, and such risks must be weighed against the clinical benefit of that medication.

Accordingly, the clinical and research use of these drugs must be undertaken with appropriate prudence in which the effect of the potential risks (e.g., cardiovascular) must be weighed against the potential beneficial effects. For treatment of conditions, for which celecoxib is being used in a hypothesis-generating setting (i.e., phase II studies, where another coxib or nonsteroidal anti-inflammatory drug has not previously shown efficacy), a similar approach should be taken. The cardiovascular safety concerns of COX-2 inhibitors became only apparent of several years of high dose use, thereby supporting their short-term use (even up to a year or longer) but likewise showing the potential risks of long-term administration. It remains unclear as to whether concomitant aspirin use in patients on long-term celecoxib therapy will provide a potential protective or beneficial effects with regard to cardiovascular safety. It is our recommendation that the use of celecoxib or other specific or nonspecific COX-2 inhibitors only be considered as part of a clinical trial using the appropriate care, caution, and informed consent as with any potentially harmful study drug.

Nevertheless, the results of this study suggest a consistent, inhibitory effect on PSA progression. An inhibitory effect was observed in a statistically significant proportion of treated patients, suggesting a nonrandom, drug effect on PSA increase. In addition, the effects observed were felt to be substantial with regard to slowing the rate of PSA increase in the short run. In fact, well over half of the treated patients had a stabilization or even a decline in their absolute PSA value initially, and most patients had significant slowing of their PSA doubling time even at 18 months of follow-up. If the effect were due to PSA variability alone, one would expect a beneficial effect to be seen in only half of the patients, and mean doubling times should remain unchanged. Thus, the findings reported herein warrant further investigation in a larger cohort of patients and with longer biochemical and clinical follow-up. Furthermore, the results of studies that evaluate the effect of celecoxib on correlative biomarkers may help enlighten the possible mechanisms of the action of these medications in prostate cancer (30).

Conclusions

COX-2 inhibitors may have an effect on serum PSA levels in patients with biochemical progression after definitive radiation therapy or radical prostatectomy. These results suggest that COX-2 inhibitors may help delay or prevent disease progression in these patients and thereby help extend the time until androgen deprivation therapy. Further study with longer biochemical and clinical follow-up is currently being undertaken to better evaluate the potential of COX-2 inhibitors as an antitumor medication in prostate cancer and to help justify if the benefits of such therapy outweigh the potential risks associated with this group of medications.
References


Phase II Trial of Celecoxib in Prostate-Specific Antigen Recurrent Prostate Cancer after Definitive Radiation Therapy or Radical Prostatectomy

Raj S. Pruthi, J. Eric Derksen, Dominic Moore, et al.


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