ORIGINAL REPORT

Celecoxib Versus Placebo for Men With Prostate Cancer and a Rising Serum Prostate-Specific Antigen After Radical Prostatectomy and/or Radiation Therapy

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A B S T R A C T

Purpose
To assess the biologic activity of celecoxib, a selective cyclooxygenase-2 inhibitor, in men with recurrent prostate cancer using change in prostate-specific antigen (PSA) doubling time (PSADT) as the primary outcome variable.

Patients and Methods
Participants had histologically confirmed prostate cancer, no recent hormone therapy, rising serum PSA after radical prostatectomy and/or radiation therapy, and no radiographic evidence of metastases. Patients were randomly assigned to celecoxib (400 mg by mouth twice daily) or placebo. Treatment continued until disease progression or until adverse effects stopped treatment. A positive outcome was defined as post-treatment PSADT of more than 200% baseline PSADT with no new metastases.

Results
The study was terminated early after information about the cardiovascular safety of celecoxib prompted review of ongoing clinical studies. Before discontinuation of the study, 78 men were assigned randomly to either celecoxib or placebo. Eight (20%) of 40 men in the placebo group and 15 (40%) of 38 men in the celecoxib group had post-treatment PSADT of more than 200% of baseline PSADT with no new metastases ($P = .08$). Mean PSA velocity increased by 3.0% for the placebo group and decreased by 3.4% for the celecoxib group ($P = .02$).

Conclusion
Although the primary efficacy objective was not met, this study provides some evidence for biologic activity of celecoxib in prostate cancer. Compared with placebo, celecoxib significantly decreased mean PSA velocity and tended to increase the proportion of men who doubled their PSADT.

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INTRODUCTION

Prostate cancer is the most common solid tumor in men worldwide. In 2005, there were approximately 232,090 new cases of prostate cancer and 30,350 prostate cancer deaths in the United States.[1] Approximately 80% of new cases are clinically localized, and most men with these early-stage prostate cancers are treated with radical prostatectomy or radiation therapy. Approximately one third to one half of patients experience disease recurrence after definitive local treatment.

Rising serum prostate-specific antigen (PSA) levels after radical prostatectomy or radiation therapy provides an early indication of recurrent disease. A serial rise of serum PSA levels after surgery or radiation therapy, however, typically predates by many years clinically or radiographically detectable metastatic disease without additional treatment. In a retrospective series of men with a rising PSA after radical prostatectomy, for example, the median time to metastasis was 8 years from the time of PSA elevation.[2]

Increases in serum PSA following radical prostatectomy or radiation therapy follow an exponential growth curve and the relationship between log PSA and time is linear.[2-4] Log-slope PSA, PSA doubling time (PSADT), Gleason grade, and the interval between local treatment and biochemical progression predict the probability of survival and the time to development of distant metastatic disease. The PSADT or the equivalent log-slope PSA are better predictors of the probability and time to clinical recurrence than preoperative PSA levels, the interval

between local treatment and rising PSA, Gleason grade, or pathologic stage.[2,3] In men with a rising PSA after radical prostatectomy, a PSADT shorter than the median value of 10 months is the most significant predictor for progression to metastatic disease found by Pound et al.[2] Similarly, a short post-treatment PSADT following radiation therapy predicts progression to metastatic disease.[3,4] PSA velocity in men with a rising PSA following definitive local treatment is significantly related to survival.[5,6]

Men with an isolated PSA recurrence after local treatment represent an ideal population for the evaluation of novel therapies based on minimal disease state, indolent natural history, and preference to avoid the adverse effects of hormone therapy. The evaluation of novel agents in this setting, however, is hampered by the lack of convenient validated end points. Overall or progression-free survival end points are impractical because of the long interval between an initial PSA increase and development of metastases. In addition, PSA response criteria commonly used in androgen-independent prostate cancer[7] may neglect biologically and potentially clinically meaningful activity, particularly with cytostatic agents. Changes in PSADT may be more sensitive to detect biologic activity than traditional PSA response criteria, although PSADT has not been adequately evaluated as a clinical trial end point.

Cyclooxygenase (COX) enzymes catalyze the synthesis of prostaglandins from arachidonic acid. The COX-1 isoform is constitutively expressed in most tissues. In contrast, COX-2 is not expressed in most normal tissues but is rapidly induced by a variety of inflammatory and mitogenic stimuli. COX-2 has been implicated in the pathogenesis of a variety of human malignancies. Preclinical and clinical evidence suggest that COX-2 is an attractive target for the treatment or prevention of prostate cancer. Some but not all studies suggest that COX-2 is overexpressed in the primary human prostate cancers and human prostate cancer cell lines.[8-12] Selective COX-2 inhibitors induce apoptosis of human prostate cancer cells in vitro and in vivo.[13,14] Lastly, treatment with nonspecific COX-2 inhibitors is associated with a lower risk of prostate cancer.[15]

Celecoxib (Celebrex; Pfizer Inc, New York, NY) is a selective COX-2 inhibitor indicated for osteoarthritis, rheumatoid arthritis, acute pain, primary dysmenorrhea, and familial adenomatous polyposis. In this study, we prospectively compared the effects of celecoxib and placebo in men with a rising PSA after radical prostatectomy and/or radiation therapy. We evaluated changes in PSADT as a screen for biologic and clinical activity.

PATIENTS AND METHODS

Study Participants

Study participants were recruited at the Dana-Farber Cancer Institute (Boston, MA), Massachusetts General Hospital (Boston, MA), Beth Israel Deaconess Medical Center (Boston, MA), The University of Texas M.D. Anderson Cancer Center (Houston, TX), Hartford Hospital (Hartford, CT), Lowell General Hospital (Lowell, MA), and the University of Michigan (Ann Arbor, MI) between October 2002 and December 2004. Participants had histologically confirmed adenocarcinoma of the prostate, biochemical disease progression after radical prostatectomy and/or radiation therapy (external-beam radiation therapy and/or brachytherapy), and no radiographic evidence of metastases. Biochemical progression was defined as three rises in PSA

levels, with each PSA determination at least 4 weeks apart, and each PSA value $\geq$ 0.2 ng/mL. Men with history of radical prostatectomy were required to have baseline PSA $\geq$ 1 ng/mL. Men treated with primary radiation therapy were required to have baseline PSA $\geq$ 3 ng/mL and postradiation nadir greater than 150%. Men with baseline PSADT $\leq$ 6 months or $\geq$ 24 months were excluded. Men with previous neoadjuvant or adjuvant hormone therapy were included if the interval between completion of hormone therapy and study entry was greater than 1 year. Men who received radiation therapy within 6 months of study entry, who received any treatment with chemotherapy for prostate cancer, or who received previous hormonal therapy for recurrent prostate cancer were excluded. Participants receiving low-dose aspirin ($\leq$ 325 mg daily) were included. Participants who received treatment with a nonsteroidal anti-inflammatory drug or COX-2 inhibitor within 8 weeks of study entry were excluded. Participants with Cancer and Leukemia Group B performance status $\geq$ 2, allergy to nonsteroidal anti-inflammatory drugs, history of gastrointestinal ulcers or bleeding within 12 months of study entry, myocardial infarction within 12 months, or current treatment with fluconazole, lithium, or warfarin were excluded. Subjects with WBC less than 3,000, absolute neutrophil count less than 1,500, hemoglobin count less than 10 g/dL, platelet count less than 100,000, creatinine level of more than 1.5 mg/mL, or serum ALT, AST, or total bilirubin $\geq$ 1.5$\times$ the upper limit of normal were also excluded.

Study Design

The study was a prospective, randomized, placebo-controlled clinical trial with optional cross-over at 6 months. Participants were stratified according to history of prostatectomy (yes v no), current use of cardioprotective doses of aspirin (yes v no), and baseline PSADT ($<$ 10 months v $\geq$ 10 months). At a baseline visit, participants underwent a physical examination, radionuclide bone scan, abdominal and pelvic computed tomography scans, ECG, complete blood count, routine serum chemistries, and serum PSA. Eligible participants were randomly assigned to treatment with celecoxib (400 mg by mouth twice daily) or placebo for 6 months. No dose or schedule modifications were permitted. Study participants and study personnel were blinded to treatment assignments. Other therapies for prostate cancer were not permitted during the study. Serum PSA was measured every 4 weeks.

Study participants continued blinded treatment for 6 months. Treatment was discontinued early for any participants with an expected Common Toxicity Criteria (CTC) grade 3 or greater toxicity, unexpected grade 3 or greater toxicity that was definitely or probably related to study drug, or progressive disease (defined in Study Outcomes section). Participants who discontinued treatment because of toxicity were withdrawn from the study. Treatment assignments were unblinded for participants who completed 6 months of treatment or discontinued early because of progressive disease. Participants assigned to placebo were eligible to cross-over to open-label treatment with celecoxib for six months. Open-label treatment was discontinued early for any subject with an expected CTC grade 3 or greater toxicity, unexpected grade 3 or greater toxicity that was definitely or probably related to study drug, or progressive disease.

The institutional review boards of each of the participating institutions approved the study. All study participants gave written informed consent. The study sponsors played no role in the study

design, in collection, analysis and interpretation of data, or in the writing of this report.

Study Outcomes

PSADT was calculated by natural log of 2 (0.693) divided by the slope of the relationship between the natural log of PSA and time.[2] Slope was calculated by linear regression. The baseline (pretreatment) PSADT was calculated using the three PSA level increases required for study entry, all other PSA values obtained during the interval between the first and third PSA level increase, and the PSA value immediately preceding the first PSA increase. The post-treatment PSADT was calculated using PSA measurements obtained at baseline and monthly for the first 6 months of treatment. For patients who discontinued treatment before 6 months, all available PSA measurements before discontinuation of treatment were used to calculate PSADT. All participants with either progressive disease or at least one post-treatment PSA measurement were considered assessable.

A positive PSADT outcome was defined as either a post-treatment PSADT of more than 200% of the baseline PSADT or a negative post-treatment PSADT (declining PSA) with no new metastases. Disease progression was defined as new evidence of metastatic disease, or PSA ≥ 200% of baseline value.

Statistical Analyses

The primary study objective was to compare the proportion of men with a positive PSADT outcome between the two groups. The study was designed to distinguish between a 65% positive outcome rate for celecoxib-treated patients and a 35% positive outcome rate for placebo-treated participants. With a target accrual of 140 participants (65 assessable participants and five unassessable participants per arm), the design provided 90% power using a two-sided Fisher's exact test with type I error of 5%.

Fisher's exact test was used to compare the proportion of men with a positive PSADT outcome between the groups. The Wilcoxon rank sum test was used to compare PSA slopes and PSA doubling times between groups. This test was also used to compare post-treatment changes in PSA slope between the groups, and to compare changes in PSA velocity between the blinded and open-label treatment period for participants assigned to placebo.

RESULTS

Participant Characteristics

In December 2004, the study was discontinued before the accrual goal of 140 participants, after information about the cardiovascular safety of celecoxib[16] prompted review of ongoing clinical studies. Before the study was discontinued, 78 men were randomly assigned to either celecoxib or placebo. Baseline characteristics including age, prior prostatectomy, and PSA were similar between the groups (Table 1). Mean baseline PSADT was 12.7 months(SD, 6.0 months) in the placebo group and 12.1 months (SD, 4.5 months) in the celecoxib group. Fourteen men (eight assigned to placebo, six assigned to celecoxib) completed less than 6 months of treatment because of early discontinuation of the study; these participants were included in the analyses.

Table 1. Participant Characteristics

Characteristic	Percentage of Participants	
	Placebo (n = 40)	Celecoxib (n = 38)
Age, years		
Mean	67	69
SD	8	7
Median	66	68
Race/ethnicity		
Non-Hispanic white	97	89
Non-Hispanic black	0	8
Hispanic	3	3
Current aspirin use	38	37
Gleason sum at diagnosis		
3-6	31	15
7	46	66
8-10	23	18
Unknown	10	11
Prior prostatectomy	60	58
Prior radiation therapy	82	68
Prior hormone therapy	35	13
PSA, ng/mL		
Mean	7.9	6.0
SD	10.1	6.8
Median	9.2	8.2
PSADT, months		
Mean	12.7	12.1
SD	6.0	4.5
Median	11.2	12.1

Abbreviations: SD, standard deviation; PSA, prostate-specific antigen; PSADT, PSA doubling time.
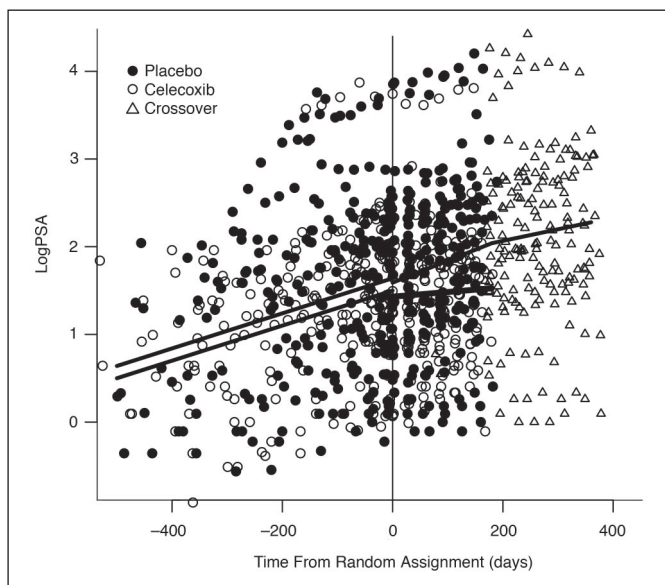
PSA Outcomes

Figure 1 shows log-PSA measurements during the pretreatment, randomized, and open-label periods for men randomly assigned to placebo and celecoxib.

Eight (20%) of 40 men in the in the placebo group and 15 (40%) of 38 men in the celecoxib group had post-treatment PSADT of more than 200% of baseline PSADT with no new metastases ($P = .08$; Table 2). Figure 2 illustrates the relationships between baseline and post-treatment PSADT for each group. The mean change in PSA velocity differed significantly between the groups. Mean PSA velocity increased by 3.0% for the placebo group and decreased by 3.4% for the celecoxib group ($P = .02$ for between-group comparison).

Twenty-nine men in the placebo group crossed over to open-label treatment with celecoxib. Ten of these men (35%) had PSADT during open-label celecoxib treatment that was more than 200% of PSADT during placebo treatment. Mean PSA velocity decreased by 7.4% after cross over to open-label treatment, although this change was not statistically significant ($P = .59$). Figure 3 shows the relationships between PSADT during placebo treatment and PSADT during open-label celecoxib treatment.

Adverse Events

There were no deaths during the study. Serious adverse events (all grade 3) were reported in four participants in the placebo group (supraventricular arrhythmia, bipolar disorder, erectile dysfunction, incontinence, and pleural effusion) and five patients in the celecoxib group (erectile dysfunction, incontinence, hypertension, sinus
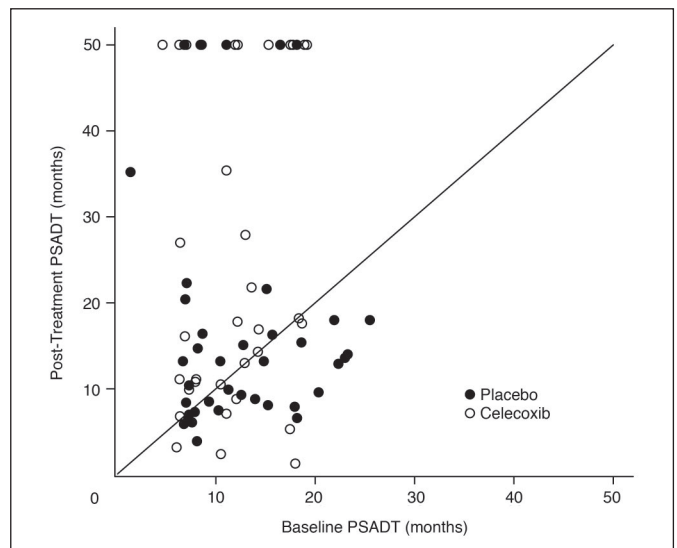
Fig 1. Log prostate-specific antigen (PSA) measurements during the pretreatment, randomized, and open-label periods for men randomly assigned to placebo (thin line) and celecoxib (thick line).

Fig 2. Relationship between baseline and post-treatment prostate-specific antigen doubling time (PSADT) for men in the placebo group (closed circles) and celecoxib group (open circles) during the blinded treatment period.

bradycardia, rash, abnormal stress test, and the detection of pulmonary nodules). These adverse events led to study discontinuation for one participant in the placebo group (bipolar disorder) and three participants in the celecoxib group (one for rash, one for abnormal stress test and pulmonary nodules, and one for hypertension and bradycardia).

DISCUSSION

We compared the effects of celecoxib and placebo on the change in PSA kinetics in men with a rising PSA after radical prostatectomy and/or radiation therapy. Although the primary study outcome was negative, there was some evidence for biologic activity of celecoxib in prostate cancer. First, more men in the celecoxib group doubled their PSADT than in the placebo group (40% v 20%; $P = .08$). Second, mean post-treatment change in PSA velocity differed significantly between the placebo and celecoxib groups (3.0% increase v 3.4% decrease; $P = .02$). Third, 35% of men in the placebo group doubled their PSADT after cross over to open-label celecoxib.

Our observations are consistent with the results of a recently reported pilot study of celecoxib in men with elevated serum PSA

levels after radical prostatectomy or radiation therapy.[17] At 6 months, five of 12 men had either stable or declining PSA. Mean PSA velocity decreased after celecoxib treatment.

Our results may have important implications about the use of PSADT or PSA velocity as a study end point. Twenty percent of placebo-treated participants had favorable outcomes, defined as post-treatment PSADT of more than 200% of baseline PSADT. In another randomized controlled trial of men with rising PSA after surgery or radiation therapy, 31% of placebo-treated participants had post-treatment PSADT of more than 200% of baseline PSADT.[18] The high rate of positive PSADT outcomes may reflect the limited precision of PSADT determinations. Alternatively, the relatively high rate of PSADT prolongation may be related to the placebo effect.[19] Mean
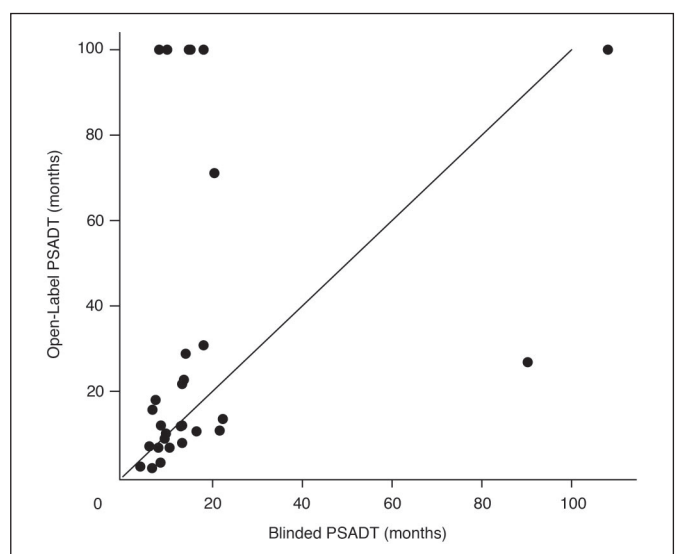
Fig 3. Relationships between prostate-specific antigen doubling time (PSADT) during placebo treatment and PSADT during open-label celecoxib treatment for the placebo group.

Table 2. Primary Efficacy Analyses

Positive PSADT Outcome	Placebo		Celecoxib		
	No. of Participants	%	No. of Participants	%	P
Yes	8	20	15	40	.08
No	32	80	23	60	

NOTE: Positive PSADT outcome was defined as post-treatment PSADT > 200% of baseline PSADT with no metastatic disease.
Abbreviation: PSADT, prostate-specific antigen doubling time.

post-treatment PSA slope did not change significantly from baseline in the placebo group, however, suggesting that the higher than expected rate of positive PSADT outcomes did not result from temporal changes in tumor growth rate. Larger studies to assess the relationship between PSA kinetics and clinical outcomes will be required to evaluate the utility of post-treatment changes in PSADT or PSA velocity in the clinical development of new drugs for prostate cancer.

Our study has limitations. The study was underpowered because of its early termination and incomplete accrual. Baseline PSADT was calculated using PSA values determined at irregular intervals, whereas post-treatment PSADT was calculated using monthly PSA values. For most participants, baseline PSADT was calculated using fewer PSA values than the post-treatment PSADT. Differences in the intervals between PSA measurements and in the number of PSA values may have contributed to the variability between baseline and post-treatment PSADT in the placebo group. We evaluated changes in PSADT as a screen for biologic and clinical activity and cannot exclude the possibility that celecoxib modulated PSA expression without altering growth or survival of prostate cancer cells. Larger studies with clinical end points would be necessary to assess whether celecoxib had meaningful clinical activity.

In summary, we observed evidence for modest biologic activity of celecoxib in men with rising PSA levels after radical prostatectomy and/or radiation therapy for prostate cancer. These results provide further rationale for the evaluation of COX-2 inhibitors in prostate cancer. When considering future clinical trials of COX-2 inhibitors for prostate cancer, however, the potential beneficial effects of COX-2 inhibition will have to be weighed against the possible increase in cardiovascular disease risk.

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Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Authors	Employment	Leadership	Consultant	Stock	Honoraria	Research Funds	Testimony	Other
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