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A Randomized Controlled Trial of Celecoxib to Prevent Recurrence of Nonmuscle-Invasive Bladder Cancer

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Abstract

Significant morbidity and expense result from frequent recurrences of nonmuscle-invasive bladder cancer (NMIBC) after standard treatment, and carcinoma *in situ* (Tis) is a poor prognostic factor. Predicated on observational and preclinical data strongly supporting cyclooxygenase-2 (COX-2) in the pathogenesis, and the activity of COX-2 inhibitors, in bladder cancer, we conducted a randomized, double-blind, placebo-controlled trial to determine whether celecoxib could reduce the time-to-recurrence (TTR) in NMIBC patients at high risk for recurrence. A total of 146 patients were randomized to celecoxib (200 mg) or placebo orally twice daily for at least 12 months. The average treatment duration was 1.25 years. Primary intent-to-treat analysis revealed celecoxib did not statistically significantly prolong TTR compared with placebo ($P = 0.17$, log rank) with a median follow-up of 2.49 years. The recurrence-free rate at 12 months with celecoxib was 88% (95% CI: 0.81–0.96) versus 78% (95% CI: 0.69–0.89) with placebo. After controlling for covariates with Cox regression analysis, recurrence rates did not differ between the two study arms (HR = 0.69; 95% CI: 0.37–1.29). However, celecoxib had a marginally significant effect on reducing metachronous recurrences (vs. placebo) with HR of 0.56 (95% CI: 0.3–1.06; $P = 0.075$). Celecoxib was well tolerated, with similar adverse events and quality-of-life in both arms. Our clinical trial results do not show a clinical benefit for celecoxib in preventing NMIBC recurrence but further investigation of COX-2 inhibitors in this setting is warranted. *Cancer Prev Res; 4(10); 1580–9. ©2011 AACR.*

Introduction

Considerable morbidity and economic burden to the health care industry result from bladder cancer (1, 2). Bladder cancer is the most frequently recurring and second most common genitourinary malignancy, with 61,000 new cases and more than 13,000 deaths in the United States annually (3). Indeed, the U.S. prevalence of all bladder cancers (>500,000 cases) has surpassed that of lung cancer (4). About 80% of all newly diagnosed cases are nonmuscle-invasive transitional cell carcinoma (TCC; ref. 5). Nonmuscle-invasive bladder cancer (NMIBC) is classified as stage Ta (papillary; 60%), T1 (superficially invasive; 30%), or carcinoma *in situ* (Tis; 10%), and histologically graded from low grade (G_1) to high grade (G_3). The typical clinical course of NMIBC is frequent recurrence and progression despite the best available treatment. A higher stage and grade (i.e., T1-G_3) confer worse prognosis, as does Tis. At least half of all low-stage, low-grade (i.e., Ta-G_1) tumors will recur and approximately 5% will progress to a higher stage. Tis alone, or in association with Ta or T1 papillary tumor, carries a poorer prognosis and a recurrence rate of 63% to 92% (6–9).

Standard treatment for NMIBC is transurethral resection (TUR) of the bladder tumor with or without adjuvant intravesical Bacillus Calmette-Guérin (BCG) immunotherapy. BCG is the most effective adjuvant therapy currently available for reducing recurrence and progression of high-risk NMIBC, and remains a first-line ablative therapy for Tis (10–12). Nevertheless, 30% to 80% of the patients treated with adjuvant BCG recur. Therefore, new approaches for preventing recurrence are needed and under investigation to control the morbidity and other consequences of bladder cancer (13, 14). Cancer chemoprevention is one such promising approach (15). NMIBC is ideal for testing new chemoprevention strategies because of its high recurrence rates and the relative ease of access to the urothelium for

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monitoring intervention effects and for obtaining tissue for biomarker assessments via cystoscopy and urine or bladder barbotage.

COX-2 garnered interest as an exciting and potentially feasible target for treatment and prevention of various cancers (16, 17) as the COX-2 molecular pathway became recognized as an important gatekeeper of downstream mediators critical to cellular proliferation, apoptosis, angiogenesis, and invasion. Evaluation of bladder cancers showed aberrantly high COX-2 expression in the majority of TCC, but not normal urothelium (18–21), and extensive animal model work provided strong support for efficacy of COX inhibitors for treatment and prevention of bladder tumors (17). Several important clinical trials subsequently showed efficacy of selective COX-2 inhibitors, such as celecoxib, in prevention of colon and nonmelanoma skin cancers. Celecoxib (compared with placebo) significantly reduced sporadic colorectal adenoma incidence in both the Prevention of colorectal Sporadic Adenomatous Polyp (Pre-SAP; ref. 22) and Adenoma Prevention with Celecoxib (APC) trials (23, 24). Celecoxib was also effective at significantly reducing nonmelanoma skin cancers by more than 50% in subjects with actinic keratosis who were randomized to celecoxib versus placebo (25). These clinical data, combined with the observational, animal-model, and mechanistic data, have generated tremendous promise for cyclooxygenase (COX) inhibitors in prevention and therapy for TCC and other cancers (16, 17, 23, 26–29).

On the basis of these supporting data and unmet clinical need, we conducted a randomized, placebo-controlled trial of celecoxib to prevent recurrence in patients with NMIBC at a high risk of recurrence after treatment with TUR and adjuvant BCG.

Patients and Methods

Patients

Patients were required to have a high risk for recurrence of TCC after transurethral resection (TUR) of the bladder tumor based on the following tumor characteristics: Stage Ta (G_3, or multifocal, or 2 or more occurrences within 12 months, including the current tumor), and/or stage T1 (any grade), and/or Tis. Eligibility criteria included histologic documentation of NMIBC, complete TUR of visible bladder tumor(s), and adjuvant "6 + 3" BCG regimen (6 weekly doses of "induction" BCG after TUR, followed by 3 weekly maintenance doses), and documentation of disease-free status (negative cystoscopy and negative urine cytology) after induction BCG. Participating patients were required to be 18 years or older, have a performance status of Zubrod 2 or less, have adequate hematologic, liver, and renal function, and to have a normal imaging study of the upper urinary tract (e.g., retrograde pyelogram or CT scan) within 9 months of randomization. Females of childbearing potential were required to have a documented negative pregnancy and to use adequate birth control for treatment duration. Cardioprotective doses ($\leq$ 100 mg daily) of aspirin were allowed. Our eligibility permitted some leniency as clinically indicated in the prescribed BCG 6 + 3 schedule as follows: for BCG intolerance, a minimum of 4 induction doses and 1 maintenance dose were required, but allowed dose reductions and/or administration on nonconsecutive weeks. We also permitted BCG treatment (remote or recent) prior to enrollment, additional induction courses of BCG (e.g., 6+ 6+3), and concurrent use of intravesical interferon. However, postrandomization BCG treatments were strictly limited to the prescribed maintenance series of 3 weekly doses) of BCG.

Exclusion criteria included: anticipated frequent use of other NSAIDs (defined as 3 times per week for more than 2 consecutive weeks per year) or chronic use of inhaled, oral or intravenous corticosteroids for the duration of study enrollment; coagulation disorder, diabetes, renal, hepatic or chronic inflammatory disease and second primary non-bladder malignancy within 5 years. Additional exclusion criteria added after the cardiovascular toxicity information was available included active cerebrovascular or cardiovascular (CV) disease, uncontrolled metabolic syndrome or a family history of premature coronary artery disease.

Trial design and randomization

This double-blinded phase IIb trial randomly assigned patients to receive celecoxib or matching placebo after confirmation of eligibility. Randomization was stratified by accrual center and by presence or absence of Tis. The primary endpoint was TTR. The predetermined secondary endpoints were toxicity and quality of life (QOL). Celecoxib (200 mg) or placebo was taken orally, twice a day for a minimum of 12 months (for the latest randomized patients) and maximum of 24 months (for the earliest randomized patients), or until histologic documentation of recurrence. Treatment also was discontinued for unacceptable or serious adverse event (AE), serious intercurrent illness (including diagnosis of a nonbladder malignancy), or pregnancy.

Clinical evaluation was done at 6 weeks after starting the study drug and every 3 months thereafter until study drug discontinuation. Clinical evaluations included a focused history and physical exam, cystoscopic examination (by a participating study-site urologist), bladder cytology, and compliance measurement (capsule count). Standard blood tests and urine for urinalysis were obtained at baseline and every 6 months. QOL assessment was made at randomization (baseline) and at 1 year or at treatment termination. An abbreviated form of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30, version 3.0; ref. 30) was utilized, which we modified with permission for specific relevance to this study. All clinically suspected cases of recurrent NMIBC required histologic verification. All primary tumors and recurrences were confirmed by a central pathology review by the study pathologist. Follow-up for all patients after discontinuation of the study drug was made by telephone by the study coordinator at each recruitment site. The first contact occurred at 30 days after study drug discontinuation to assess AEs, bladder cancer status,

smoking status, and NSAID use. Off-drug telephone follow-up continued every 3 months until study closure, with a case–report form filed for each contact.

The clinical trial was conducted at multiple recruitment centers in the United States (see Appendix). The University of Texas MD Anderson Cancer Center served as the lead institution. All participating sites were required to receive the approval of their Institutional Review Board before initiating the study.

Statistical analysis

The planned sample size was 152 patients (76 per arm) and was calculated assuming that approximately 34% of patients in the placebo arm would recur within 12 months and 45% would recur within 24 months (after TUR and BCG), assumptions based on data from our clinical experience at MD Anderson Cancer Center and previous studies (31). The study was designed to have 80% power to detect a 53% reduction in recurrence at 12 months, from 34% in the placebo arm to 16% in the celecoxib arms, with a significance level of 0.05 (log-rank test). We assumed a constant hazard ratio (HR), a minimum accrual period of 12 months, a minimum follow-up of 12 months, and a drop-out rate of 5%. The study was scheduled to end when the last enrolled patient either completed 12 months of study drug or had a documented recurrence. This study design enhanced the number and duration of patients on study to capture the most events. If patients entered the study at an expected constant rate more than 12-month accrual period, then at least 33% of the patients would have the opportunity to remain on study for 24 months. An interim analysis was planned for when half of the patients had been followed for 12 months. Early termination of the study was planned if the difference in proportions of recurrence between the 2 groups was statistically significant at $P < 0.001$.

The primary analysis was an intent-to-treat (ITT) analysis, defined as including all randomized patients. The Kaplan–Meier method was used to estimate the primary endpoint TTR function. We defined the date of recurrence as the date of the biopsy that yielded a histologically confirmed recurrence (although the actual recurrence could have occurred between the last disease-free visit and the date of confirmed recurrence). The Cox regression model stratified by Tis stage was employed to estimate the treatment effect by adjusting for the effects of other covariates known (or believed) to be of prognostic importance, such as tumor stage and grade, use of cardioprotective-dose aspirin, and smoking history. All patients who exited the study with a histologically confirmed bladder cancer recurrence reached the study endpoint. Patients who exited the study without recurrent disease were censored observations. Patients who died for reasons unrelated to study treatment without recurrence were considered censored observations at the time of their death.

To supplement the primary analysis, a secondary analysis of the treatment effect of celecoxib on multiple recurrences was analyzed in the multivariate survival model proposed by Wei and colleagues (32). QOL analysis in the ITT population utilized a generalized estimation equation model to analyze differences in responses to each QOL question between the celecoxib and placebo arms. Overall compliance was followed by and calculated from capsule counts. Wilcoxon rank sum test and Chi-square tests were applied to compare the compliance between the two arms. We also conducted the analysis of TTR in the perprotocol population, which comprised randomized patients who met the inclusion/exclusion criteria, had available data for at least 1 cystoscopic evaluation and were at least 80% compliant with study medication.

Results

Accrual and patient characteristics

Between June 23, 2000 and March 15, 2005, 146 patients were accrued at 29 study sites and were randomly assigned to receive celecoxib or placebo (Fig. 1). This accrual period comprised a National Cancer Institute–mandated moratorium on accrual from mid-December 2004 through February 2005 due to concerns over celecoxib's potential CV toxicity that were raised in the setting of colorectal adenoma prevention (33, 34); 146 patients had been randomized prior to, and patients were allowed to continue study drug during, the accrual moratorium. Patients on study when accrual was interrupted received the new safety information

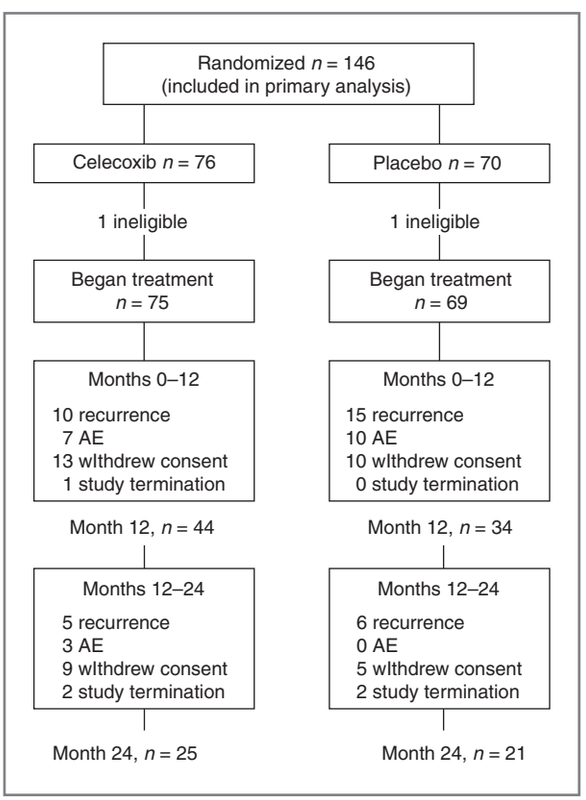

Figure 1. CONSORT diagram showing the flow of patients through the trial from randomization through the end of 2 years, which was the maximum time a patient was allowed to receive treatment.

by phone and in writing. Those on study drug were given the option to continue or discontinue the study drug. Patients who consented to continue on study drug were required to sign an updated consent form detailing the information on CV risk. Three patients in each arm not experiencing AEs stopped study medication because of this new toxicity information. Patients who discontinued the study treatment continued follow-up until study termination unless consent was withdrawn. The study was closed after randomization of 146 of the planned 152 patients at the recommendation of the Data Monitoring Committee (DMC) after the planned (albeit delayed) interim analysis of the 146 patients showed that completing planned accrual would not significantly alter the interim results.

Major characteristics of the overall population of 146 patients were well balanced in the 2 arms, except for a history of hypertension, which was significantly more prevalent in the placebo arm ($P = 0.01$; Table 1). All other factors known or believed to be of prognostic importance (but not used for stratification) were distributed equally between the 2 study arms (Tables 1 and 2).

Figure 1 depicts the flow of patients through the trial, from randomization to 12 and 24 months of treatment. Reason indicated for not starting the study drug was ineligibility (1 celecoxib, 1 placebo). All 146 randomized patients were included in the ITT analyses, and 110 randomized patients in the perprotocol analysis. Among the patients who began treatment, the reasons for terminating study drug early, or prior to completing 12 months of treatment, included recurrence (10 celecoxib, 15 placebo), AEs (7 celecoxib, 10 placebo), consent withdrawal (13 celecoxib, 10 placebo), and study termination (1 celecoxib). For those who continued study drug beyond 12 months, reasons for terminating drug prior to 24 months (maximum allowed) included recurrence (5 celecoxib, 6 placebo), AEs (3 celecoxib, 0 placebo), consent withdrawal (9 celecoxib, 5 placebo), and study termination (2 celecoxib, 2 placebo; Fig. 1). Approximately 1/3 (46/146) of all randomized patients completed 24 months of treatment, including 21 in the placebo arm and 25 in the celecoxib arm. Fourteen patients were on treatment when the study was terminated (on March 15, 2005), 8 in the placebo arm, and 6 in the celecoxib arm. The average duration on treatment was 1.25 years (1.28 years for the celecoxib arm, and 1.22 years for the placebo arm).

NMIBC recurrence

The Kaplan–Meier plots of the primary study endpoint TTR (measured from randomization to time of histologically documented recurrence) for the ITT population (all randomized patients) showed that celecoxib delayed the average TTR from 1.74 years (placebo) to 2.86 years (celecoxib), although the delay was not statistically significant ($P = 0.17$, log rank; Fig. 2). The median follow-up was 2.49 years for all censored patients, and recurrences occurred in 21/76 (27.6%) patients on the celecoxib arm and in 27/70 (38.6%) patients on the placebo arm. When we used Cox regression analysis stratified by presence or absence of Tis to control for covariates such as tumor grade, cardioprotective aspirin use (while on study), prior regular use of NSAIDs, and smoking, the recurrence rates in the ITT population did not differ significantly between the celecoxib and placebo arms with HR for recurrence of 0.69 (95% CI: 0.37–1.29, $P = 0.25$; Table 3).

The recurrence-free rates at 12 months, were 88% (95% CI: 0.81–0.96) in the celecoxib arm and 78% (95% CI: 0.69–0.89) in the placebo arm and at 24 months were 74% (95% CI: 0.64–0.86) in the celecoxib and 60% (95% CI: 0.49–0.73) in the placebo arm. Interestingly, of the patients with Tis, 100% (15/15) who took celecoxib were recurrence free at 12 months, whereas only 77% (10/13) who took placebo were without recurrence at 12 months. Significance of this subgroup could not be determined due to small numbers. Because NMIBC tends to recur repeatedly, we also evaluated effect of celecoxib on metachronous recurrences. Although being followed on study, 48 patients had at least 1 recurrence. Of the patients with at least 1 recurrence, 11 patients had more than 1 recurrence (7 recurred twice, and 2 patients had 3 recurrences, and 2 patients had 4 recurrences). Using the method of Wei and colleagues (32), we found that celecoxib marginally significantly reduced the risk of subsequent recurrences compared with placebo (HR = 0.56; 95% CI: 0.30–1.06; $P = 0.075$).

The perprotocol population (defined in Methods) of 110 patients was analyzed and results did not differ significantly from the ITT analyses. The median follow-up for the censored patients in this group was 2.59 years. The 12-month recurrence-free rate was 0.88 (95% CI: 0.80–0.96) in the celecoxib arm and 0.82 (95% CI: 0.71–0.92) in the placebo arm (log-rank test, $P = 0.58$). When we controlled for other prognostic factors (same as ITT analysis), using Cox regression analysis stratified by Tis we found that the HR of celecoxib for recurrence (compared with placebo) was 0.83 (95% CI: 0.38–1.78; $P = 0.63$).

Compliance

Overall medication compliance (Table 4) was a median of 93.3% in the celecoxib arm [$n = 75$ and 91.0% in the placebo arm ($n = 65$; Wilcoxon test $P = 0.18$)]. Compliance was high (defined as $\geq$ 80%) in 80.3% of patients in the celecoxib arm and 70.0% of patients in the placebo arm (χ^2 test $P = 0.14$). The overall drug discontinuance rate was less than 5%.

Toxicity

A total of 449 AEs were recorded during this study, including 60 (13.4%) grade 3 or more events. Sixteen patients in the celecoxib arm had grade-3 events or more (Table 5), of which 2 probably were related to study medication—a grade-4 gastrointestinal disorder and a grade-3 vascular disorder. No deaths occurred while on study drug, although 15 deaths, including 9 in the celecoxib arm and 6 in the placebo arm, were reported for patients followed after study drug discontinuation. Of the 9 deaths in the celecoxib arm, 3 were attributed to progressive TCC and 6 were not, including 1 attributed to cerebrovascular disease, 2 to a

Table 1. Patient characteristics

Variable		Frequency				
		Celecox	Plbo	Total	Percent	*P*
Gender	Female	12	12	24	16.44	0.82
	Male	64	58	122	83.56	
	Total	76	70	146	100	
Race	Caucasian	69	63	132	90.41	0.87
	Asian	1	1	2	1.37	
	Black	3	0	3	2.05	
	Hispanic/ Latin American	3	4	7	4.79	
	Native American	0	2	2	1.37	
	Total	76	70	146	100	
Weekly doses of BCG	1	8	2	10	6.85	0.10
	2	3	6	9	6.16	
	3	64	58	122	83.56	
	Other	1	4	5	3.42	
	Total	76	70	146	100.00	
Previous NSAID use	No	65	63	128	87.67	0.41
	Yes	11	7	18	12.33	
	Total	76	70	146	100.00	
Take aspirin? ($\leq$100 mg/d)	No	50	45	95	65.07	0.85
	Yes	26	25	51	34.93	
	Total	76	70	146	100.00	
Hypertension	Missing	0	1	1	0.68	0.01
	1: No	41	23	64	43.84	
	2: Yes, history	1	4	5	3.42	
	3: Yes, current	34	42	76	52.05	
	Total	76	70	146	100.00	
Alcoholic drinks per day	1: None	29	28	57	39.04	0.42
	2: < = 1	26	23	49	33.56	
	3: 2–3	5	6	11	7.53	
	4: > = 4	16	13	29	19.86	
	Total	76	70	146	100.00	
Smoking status	1: Never	16	17	33	22.60	0.07
	2: Former	41	46	87	59.59	
	3: Current	19	7	26	17.81	
	Total	76	70	146	100.00	
Zubrod/ECOG performance status	0: Fully active	72	65	137	93.84	0.64
	1: Restricted but ambulatory	4	5	9	6.16	
	Total	76	70	146	100	
Stage	Ta	42	36	78	53.42	0.41
	T1	17	20	37	25.34	
	T1 + Ta	2	1	3	2.05	
	T1 + Tis	0	3	3	2.05	
	TisS	11	8	19	13.01	
	Ta + Tis	4	2	6	4.11	
	Total	76	70	146	100	

second primary lung cancer, and 3 to other central nervous system events (progressive dementia, complications from chronic alcoholism, and fatal head injury from a fall). Of the 6 deaths on the placebo arm, 1 was attributed to progressive TCC and 5 were not, including one attributed to myocardial infarction, 3 to complications of second malignancies (breast cancer, bowel infarction in the post-op setting of second primary lung cancer, and extensively metastatic small-cell lung cancer), and 1 to an unknown cause. Three deaths (1 on celecoxib, 2 on placebo) occurred during or within 30 days after discontinuing study treatment. The celecoxib-arm death was attributable not to

Table 2. Number and grade of tumor by treatment

	Number of tumor					
Tumor stage	**Ta**		**T1**		**Tis**	
Number of tumor	< = 3	>3	< = 3	>3	< = 3	>3
Celecoxib	35	4	13	2	2	1
Placebo	33	2	22	2	2	0
Grade of tumor						
Tumor stage						
Tumor grade	< = 2	>2	< = 2	>2	< = 2	>2
Celecoxib	29	13	6	13	3	1
Placebo	25	11	10	14	1	1

Abbreviations: Ta = tumor stage is Ta; T1 = tumor stage is T1, T1 + Ta, or T1 + Tis; Tis = tumor stage is Tis or Tis+Ta.

celecoxib but to complications from chronic alcoholism. The placebo-arm deaths were due to surgical complications from second primary non–small cell lung cancer in one case and to widely metastatic small-cell lung cancer in the other. The interim analysis showed no difference in CV toxicity between the study arms.

QOL (based on 18 questions about patient life and health conditions) found no statistically significant difference between celecoxib and placebo. However, patients receiving celecoxib were more likely to rate their "overall health during the past weeks" (from the QOL questionnaire) as worse ($P = 0.09$). Estimated odds of a patient rating his or her health condition below any fixed level in the celecoxib arm were 1.58 times the estimated odds of this rating in the placebo arm. This questionnaire had patients rate their health condition on a scale from 1 to 7, with worse scores on the lower end of the scale (cumulative logit link function was used in the generalized estimation equation model).

Discussion

We herein report results of the first randomized phase II study to examine the effect of a selective COX-2 inhibitor, celecoxib, on NMIBC recurrence in patients who had completed standard treatment with TUR and adjuvant intravesical BCG. Our double-blind trial randomized 146 NMIBC patients at high risk for recurrence to celecoxib or placebo for a minimum of 12 months. The primary endpoint analysis showed no statistically significant delay to in the TTR with celecoxib ($P = 0.17$), although a nonstatistically significant trend toward prolongation of average TTR was observed with celecoxib (2.86 years) versus with placebo (1.74 years), Time to recurrence when stratified for Tis and controlled for covariates, was also not statistically significant between the 2 treatment groups ($P = 0.25$). Analysis of those patients who suffered metachronous recurrences while being followed on study (after discontinuing drug at their first recurrence), showed a marginally statistically significant reduction in subsequent recurrence favoring celecoxib with a HR 0.56 (95% CI: 0.30–1.06, $P = 0.075$).

A plethora of data exist to support of the rationale and potential utility of celecoxib in bladder cancer, including mechanistic, animal, and human trials data (17–21, 35–37). Several identifiable potential influencing factors, including the utilized dose of drug, may have played a role in our failure to detect a significant benefit for celecoxib in this setting. Landmark positive clinical trials in the prevention setting have utilized a range of celecoxib dose and schedule. Our study dose (celecoxib 200 mg orally twice daily) was based on the safety data available at the time we

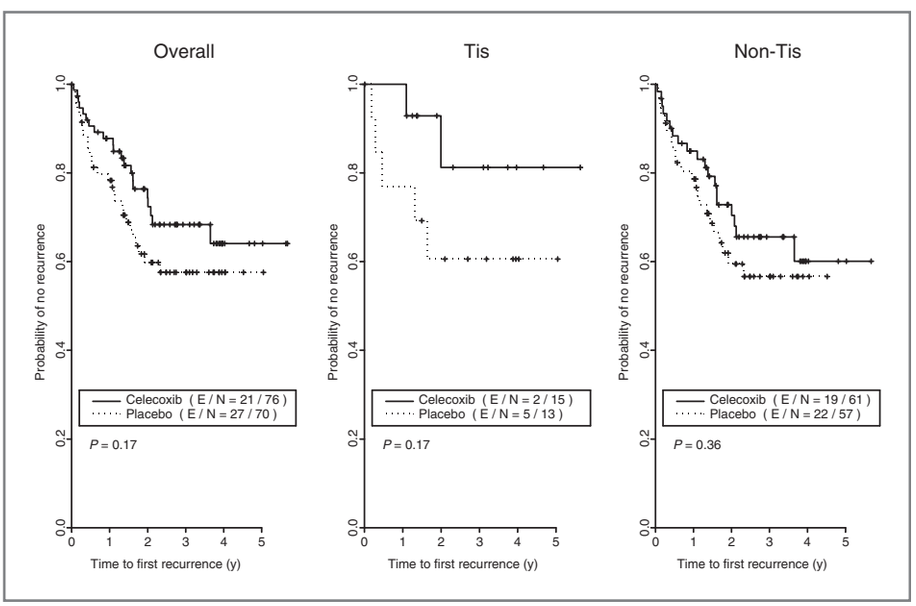

Figure 2. Kaplan–Meier plots of the time to recurrence by intervention arm (ITT) with and without stratification by the presence of Tis. E/N = Number of events/sample size.

Table 3. Stratified Cox regression model for ITT population. The stratification factor is the presence or absence of Tis

Variable	Estimate	SE	*P*	HR (95% CI)
Treatment[a]	−0.37	0.32	0.25	0.69 (0.37–1.29)
Tumor grade	−0.13	0.19	0.50	0.88 (0.61–1.27)
Aspirin (≤100 mg/d)	0.08	0.35	0.81	1.09 (0.55–2.14)
NSAID	0.35	0.43	0.42	1.42 (0.61–3.29)
Previous smoker[b]	−0.43	0.49	0.38	0.65 (0.25–1.70)
Current smoker[b]	−0.46	0.38	0.23	0.63 (0.30–1.33)

[a]Placebo arm is taken as the reference group; [b]nonsmoker is taken as the reference group.

designed the study. Several other studies utilizing the same daily dose and approximate duration of celecoxib showed efficacy in prevention of invasive squamous cell carcinoma of the skin (25), and sporadic colorectal adenomas in the PreSAP study (400 mg orally in 1 dose per day; ref. 22) and the APC trial (200 mg orally twice a day; ref. 23). However, a dose–response effect of celecoxib, with higher doses being more effective, has also been shown in several placebo controlled studies. The APC trial (23) showed a statistically improved risk ratio (RR) with a higher dose of 400 mg twice a day, compared with the 200 mg twice a day. In the Familial Adenomatous Polyposis study a significant reduction in polyp burden was seen in the higher celecoxib dose group of 400 mg twice daily but not in the lower dose group of 100 mg twice a day (38). These findings imply that that drug dose may heavily influence study outcome in certain diseases, and would need to be further investigated in bladder cancer to elucidate the relative importance in this setting.

However, the limitation to dose escalation is the observed drug toxicity. Despite being developed to improve the toxicity profile and tolerability of nonselective COX inhibitors, significant concern regarding CV safety of celecoxib has been raised (23, 39, 40), and the risk may be dose dependent with an absolute and relative increase in adverse outcomes in the presence of baseline CV risk (34, 41). Although we did not find evidence of an increased CV toxicity with celecoxib compared with placebo in our study cohort, this population is generally at high risk for cardiovascular disease, as they are a predominantly older, male, and tend to be smokers. To safely utilize COX-2 selective inhibitors with confidence in the bladder cancer and other prevention settings in the future, it will be imperative to optimize the risk-benefit ratio by taking into account dose tailored to the study cohort.

An interesting finding from our study was that recurrence risk was reduced to a greater extent in the patients with multiple observed recurrences, an effect that achieved marginal statistical significance (HR = 0.56, 95% CI: 0.3–1.06; $P = 0.075$). The estimated recurrence-free survival rates at 1 and 2 years respectively in the celecoxib arm (0.88 and 0.74), were higher than in the placebo arm (0.78 and 0.60) but did not meet statistical significance. Nonetheless, these findings are intriguing especially when taking into account that 100% of patients with Tis in the celecoxib group versus 77% in the placebo group were disease free at 12 months (numbers too small for statistical evaluation). These findings may suggest that the high-risk Tis pathology trends toward higher sensitivity to celecoxib. The effect of celecoxib on high- and low-grade bladder cancer cell lines have been minimally studied, but the available information suggests that the mechanistic response to celecoxib may differ according to bladder tumor grade (42, 43), resulting in potential differential sensitivity. Gee and colleagues (43) found that celecoxib-induced apoptosis and G_0/G_1 cell-cycle arrest occurred primarily through altered cyclin B1/D1 expression in the low-grade bladder cancer cell line (RT-2), whereas it was through Rb upregulation in the high-grade cell line (UM-UC-3). Although these are limited *in vitro* findings, it is interesting to postulate that a heterogeneous mechanistic effect dependent on the degree of cellular differentiation could alter biological susceptibility to celecoxib. These findings could be further explored to address mechanism of action or effect in the high-grade, high-risk Tis subgroup.

Table 4. Compliance[a]

Treatment	*n*	Minimum	Maximum	Median	Mean	SD
Celecoxib	75	0.0	101.2	93.3	88.3	15.2
Placebo	65	0.0	107.5	91.0	83.8	20.3
Wilcoxon test P = 0.18						

[a]For entire treatment period for each subject.

Table 5. Toxicity

Summary of the highest toxicity grade per patient

	Frequency			
Toxicity	Celecoxib	Placebo	Total	Percent
Grade 1	25	12	37	33.3
Grade 2	19	24	43	38.7
Grade 3	9	9	18	16.2
Grade 4	7	6	13	11.7
Total	60	51	111	100

Adverse events attributable to treatment

	Frequency			
	Celecoxib	Placebo	Total	Percent
None	188	195	383	85.3
Probable	10	3	13	2.9
Uncertain	24	29	53	11.8

We recognize the limitations of our study include a large estimated effect size anticipating a 53% reduction in TTR at 12 months, hence, the resulting sample size yields a lower statistical power for a smaller effect size. The unexpected temporary suspension of accrual and participant dropout due to concern for celecoxib's cardiovascular toxicity had a potential negative effect on the trial, because, although accrual was allowed to resume after a hiatus, no additional patients were accrued, leading to closure of the study 6 patients shy of the accrual goal.

Given the excellent tolerance of celecoxib in this study, it is feasible to continue to study COX-2 inhibitors in the setting of bladder cancer. In design of future clinical trials, it would be of great interest to be able to identify specific cohorts with a high chance of benefit, or specific molecular predictors of response to COX-2 inhibitors, or other investigational agents. In doing so, invaluable benefit could be gained by significant reduction of the required sample size, facilitating conduct of such studies, and potentially improving the risk—benefit ratio by choosing cohorts that might be at reduced risk for intervention-related side effects. Addressing this difficult question will likely require molecular studies of prognostic (recurrence risk) and predictive (drug sensitivity or resistance) markers, including pharmacogenomics. As well, it may lend itself to study agent combinations, new approaches to screening for active agents, and for selecting specific therapies for individual patients (personalized medicine with regard to drug benefit and risk). Research in this arena is underway.

Recent data in NMIBC suggest that hedgehog pathway single-nucleotide polymorphisms are prognostic and may be predictive of treatment outcome (44), and that high COX-2 expression in colorectal, and lung neoplasia may predict a favorable outcome of treatment with celecoxib and other NSAIDs (45, 46). Molecular studies conducted by our group and others (47–49), including identification of the molecular mechanisms and biomarkers involved in pathogenesis of TCC, and our ongoing analysis of correlative urine-based biomarkers from this trial are other examples of active efforts toward identification of potential prognostic and predictive factors of bladder carcinogenesis that hold promise for eventual clinical application.

Substantial efforts to identify new agents or agent combinations, as well as prognostic and predictive molecular markers, for reducing the recurrence of NMIBC are warranted by the major clinical and economic burdens of this disease (1, 2, 4, 50). Promising avenues of research for future preclinical and/or clinical studies might include agents showed to have a low toxicity profile in NMIBC such as fenretinide (51) or difluoromethylornithine (52) combined with a COX-2 inhibitor, other NSAID, or epidermal growth factor receptor tyrosine kinase inhibitor, and perhaps utilization of other targeted agents and novel molecular approaches which are currently being investigated (29, 44, 45, 53).

In conclusion, our study did not show a clear benefit for reduction of NMIBC recurrence with celecoxib, and these results do not support utilizing celecoxib outside of a clinical trial for NMIBC. Chemoprevention studies evaluating new approaches for reducing recurrence and progression of bladder TCC are needed. The trend of benefit we observed in the high-risk Tis group may warrant further study. The widespread interest in the selective COX-2 inhibitors for treatment and prevention of cancers, and a plethora of favorable preclinical and clinical data supporting this class of agents in a prevention setting, provide compelling evidence for further evaluation of this class of agents in bladder cancer. Future plans for study of selective COX-2 inhibitors in TCC may partially hinge on the eagerly awaited results of the Bladder COX-2 Inhibition Trial (BOXIT) which is a phase III randomized placebo controlled clinical trial of 400 patients currently ongoing in the United Kingdom. It is designed to determine whether celecoxib (400 mg daily) administered following standard treatment is superior to standard treatment alone (placebo arm) for reducing recurrence at 3 years (primary endpoint) in patients with intermediate-to-high-risk NMIBC. The accrual of BOXIT is anticipated to be completed at the end of 2011.

Appendix

The following 29 sites participated in the accrual and conduct of this trial (in order of accrual contribution): Ronald Castellanos, MD, Clinical Physiology Associates, Fort Myers, FL; Franklin Chu, MD, San Bernardino Urology Associates, San Bernardino, CA; Seth P. Lerner, MD, Baylor College of Medicine, Houston, TX; Anita L. Sabichi, MD, The University of Texas MD Anderson Cancer Center; Daniel R. Salzstein, MD, Urology San Antonio Research, San Antonio, TX; Lawrence Karsh, MD, Western Urologic Research Center, Denver, CO; John Corman, MD, Virginia Mason Medical Center, Seattle, WA; Harvey Taub, MD,

UroSearch of FL, LC, Ocala, FL; Walter Pittman, MD, Urology Centers of Alabama, Birmingham, AL; Arthur Sagalowsky, MD, The University of Texas Southwest Medical Center at Dallas, Dallas, TX; Jerrold Sharkey, MD, Advanced Research Institute, New Port Richey, FL; Gary Steinberg, MD, Louis A. Weiss Memorial Hospital, Chicago, IL; Stacy Childs, MD, Cheyenne Urological, P.C., Cheyenne, WY; Hugh A. G. Fisher, MD, Albany Medical Center South Clinical Campus, Albany, NY; Robert Feldman, MD, Urology Specialists, Waterbury, CT; Joseph Schmidt, MD, University of California, San Diego Medical Center, San Diego, CA; Alfred Sidhom, MD, Advanced Urology Medical Center Anaheim, CA; Gerald Andriole, MD, Washington University School of Medicine, St. Louis, MO; Laura Crocitto, MD, City of Hope, Duarte, CA; Mitchell Efros, MD, AccuMed Research Associates, Garden City, NY; William Monnig, MD, Tri-State Urologic Services PSC, Inc., Florence KY; Myron Murdock, MD, Research Associates, Greenbelt, MD; Isaac J. Powell, MD, Wayne State University, Detroit, MI; Paul F. Shellhammer, MD, Devine Tidewater Urology, Norfolk, VA; Richard Harkaway, MD, Albert Einstein Medical Center, Philadelphia, PA; George Kornitzer, MD, Newton Wellesley Urology, Newton, MA; Michael Manyak, MD, The George Washington University Medical Center, Washington, DC; Jay Young, MD, South Orange County Medical Research Center, Laguna Woods, CA; and Norman Zinner, MD, Doctors Urology Group, Torrance, CA.

Disclosure of Potential Conflicts of Interest

A.L. Sabichi is the consultant and advisory board member of PDQ NCI Advisory Board.

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