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Reduced bladder cancer recurrence rate with cardioprotective aspirin after intravesical bacille Calmette–Guérin

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OBJECTIVE

To evaluate the recurrence-free survival (RFS) rate of patients taking cardioprotective aspirin after intravesical bacille Calmette-Guérin (BCG) for high-grade noninvasive urothelial carcinoma of the bladder, as preventing the recurrence of superficial bladder cancer might decrease patient morbidity and mortality from this disease, and nonsteroidal anti-inflammatory agents (NSAIDs) have shown promise in preclinical prevention through inhibition of the prostaglandin pathway and other mechanisms.

PATIENTS AND METHODS

In all, 43 patients with carcinoma *in situ* (CIS) and/or high-grade papillary bladder cancer were treated with intravesical BCG. Patients were stratified according to whether they took cardioprotective aspirin after treatment, and Kaplan-Meier curves of RFS were compared by log-rank analysis. Multivariable analysis was used for potentially confounding factors, including maintenance BCG, the presence of CIS, and smoking status.

RESULTS

Of patients taking cardioprotective aspirin, the 5-year RFS rate was 64.3%, compared with 26.9% for patients not taking aspirin, with a significantly higher RFS by univariable log rank analysis ($P = 0.03$). Even after adjusting for the other factors by multivariable analysis, aspirin seems to affect recurrence (hazard ratio 0.179, $P = 0.001$). Maintenance BCG (hazard ratio 0.233, $P = 0.02$) and smoking history (hazard ratio 3.199, $P = 0.05$) also significantly affected recurrence.

CONCLUSION

There was a significantly higher RFS rate in patients taking cardioprotective aspirin after intravesical BCG therapy for bladder cancer. The results of this study support the further investigation of aspirin and other NSAIDs as preventive agents in patients being treated for superficial bladder cancer.

KEYWORDS

bladder cancer, chemoprevention, aspirin, nonsteroidal anti-inflammatory drugs, BCG

INTRODUCTION

Bladder cancer is the second most common malignancy of the genitourinary tract. During 2008 alone, ≈68 810 new cases will be diagnosed, with an estimated 14 100 deaths occurring in the USA as a result of this disease [1]. About 70% of patients present with non-muscle-invasive bladder tumours that can frequently recur and could potentially progress to muscle-invasive disease. Of these patients, those with carcinoma *in situ* (CIS) and high-grade papillary bladder cancer are at greatest risk and are followed closely by regular cystoscopic evaluation [2]. As such, this closely monitored group of patients at high risk of tumour recurrence and progression represents an ideal cohort for evaluating chemopreventive agents.

NSAIDs have shown promise in cancer prevention, presumably through inhibition of cyclooxygenase (COX)-2 and the prostaglandin pathway, and other mechanisms. Aberrant expression of COX-2 has been identified in many tumour types, including bladder cancer. This enzyme is thought to contribute to the malignant phenotype and has been implicated in increased growth, invasion, angiogenesis and resistance to apoptosis. NSAIDs are known to inhibit this enzyme, in which both selective COX-2 inhibitors and nonselective COX inhibitors have been evaluated in chemoprevention studies [3].

Interestingly, aspirin is an NSAID frequently administered in the population with bladder cancer as a cardioprotective agent, regardless of these recent chemopreventive strategies. While epidemiological studies of NSAID use and bladder cancer risk are mixed, two studies evaluating aspirin specifically have shown potential benefit of this agent [4,5]. Here we evaluate the recurrence-free survival (RFS) rate of patients taking cardioprotective aspirin after intravesical BCG therapy for high-grade noninvasive urothelial carcinoma of the bladder.

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FIG. 1. (a) RFS, Kaplan-Meier plot (P = 0.03, log-rank analysis); (b) PFS, Kaplan-Meier plot (P = 0.4, log-rank analysis).

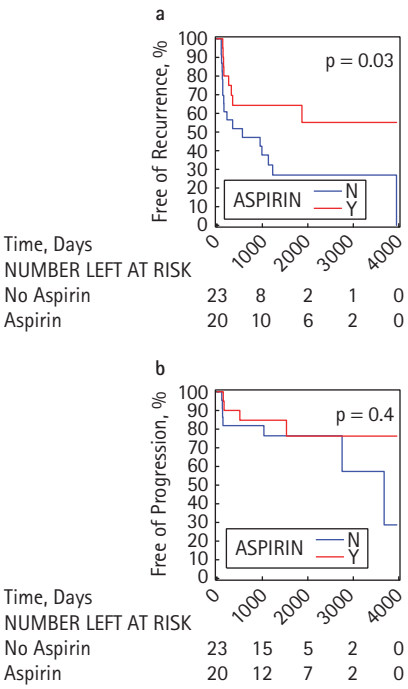

TABLE 1 Patient demographics, and the recurrence and progression rates

Variable	Aspirin (20)	No aspirin (23)	*P*
Mean age at diagnosis, years	72	63	0.009
Male, *n* (%)	18 (90)	18 (78)	0.421
Maintenance BCG	3 (15)	6 (26)	0.467
Presence of CIS	15 (75)	21 (91%)	0.222
Papillary tumour present	8 (40)	3 (13%)	0.078
Pure papillary tumour	3 (15)	1 (4%)	0.390
Current smoker	4 (20)	7/22 (32)	0.491
History of smoking	14 (70)	17/22 (77)	0.730
History of bladder cancer	9 (45)	10 (43)	1.000
Recurrence and progression rates			
Recurrence, *n* (%)	8 (40)	17 (74)	
5-year RFS rate, %	64	27	0.030
Progression, *n* (%)	4 (20)	7 (30)	
5-year PFS, %	85	76	0.407

Variable	Hazard ratio (95% CI)	*P*
Aspirin use	0.179 (0.062, 0.516)	0.001
Male	2.406 (0.656, 8.823)	0.185
Maintenance BCG	0.233 (0.069, 0.790)	0.019
Presence of CIS	0.129 (0.012, 1.384)	0.091
Papillary tumour present	0.301 (0.035, 2.570)	0.272
Pure papillary tumour	1.871 (0.228, 15.322)	0.560
Current smoker	0.270 (0.082, 0.889)	0.031
History of smoking	3.199 (0.981, 10.433)	0.054
History of bladder cancer	0.827 (0.328, 2.083)	0.687

TABLE 2 Multivariable analysis of risk factors associated with recurrence

PATIENTS AND METHODS

Using a protocol approved by the institutional review board for bladder cancer clinical-translational studies, data were obtained from a series of 154 patients with bladder cancer who had intravesical therapy at the University of Wisconsin Hospital and Clinics from June 1991 to September 2003; 46 patients from this series with CIS and/or high-grade papillary bladder cancer were treated with intravesical BCG, 43 of whom had data available and form the basis of this analysis.

Patients were stratified according to whether they took cardioprotective aspirin after treatment, defined in this study as any patient taking aspirin for most (≥50%) of the interval between diagnosis and the date of first tumour recurrence or last follow-up. Patients taking either 81 or 325 mg aspirin were included in the aspirin group. Tumour progression was also determined for these groups. Kaplan-Meier RFS and progression-free survival (PFS) curves were compared by log-rank analysis. Multivariable analysis was used to adjust for potentially confounding factors, including maintenance BCG, the presence of CIS, a history of bladder cancer, and smoking status. The presence of papillary tumour was also documented to account for the possibility of incomplete resection. The patients' characteristics are listed in Table 1.

RESULTS

Of patients taking cardioprotective aspirin, the 5-year RFS rate was 64% vs 27% for patients not taking aspirin, with a significantly higher RFS rate by univariable log-rank analysis ($P = 0.03$). The Kaplan-Meier plot for this analysis is shown in Fig. 1a. Eight of the 20 patients (40%) taking aspirin eventually had a recurrence, vs 17 of the 23 (74%) who did not take aspirin (Table 1).

Given the probable influence of other factors affecting recurrence, multivariable analysis was used to evaluate recurrence in relation to smoking status and the use of maintenance BCG. Furthermore, the presence of CIS was evaluated as a risk factor for recurrence, as was the presence of papillary tumour, as incomplete resection could potentially affect the results. Except for patient age, there were no significant differences in the subsets shown in Table 1 between patients taking or not taking cardioprotective aspirin. Three of 20 (15%) in the aspirin group were administered maintenance BCG, vs six of 23 (26%) not taking aspirin. CIS was present in 15 of 20 (75%) patients on aspirin, vs 21 of 23 (91%) not taking aspirin, whereas eight of 20 (40%) had papillary tumour at initial diagnosis, vs three of 23 (13%) in these groups, respectively. Of the patients taking aspirin, four of 20 (20%) were smokers, vs seven of 23 (30%).

Even after adjusting for the other factors by multivariable analysis, aspirin seems to have an effect on recurrence rate (hazard ratio 0.179, $P = 0.001$). Maintenance BCG (hazard ratio 0.233, $P = 0.02$) and smoking history (hazard ratio 3.199, $P = 0.05$) also significantly affected recurrence rates (Table 2).

Disease progression was also determined for these patients, as defined by progression in stage to lamina propria invasion or more

advanced stages. Progression events occurred in four of 20 (20%) patients in the aspirin group, vs seven of 23 (30%) in those not on aspirin (Table 1). However, these were not significantly different by log-rank analysis ($P = 0.41$, Fig. 1b).

DISCUSSION

NSAIDs have shown efficacy in preclinical studies of bladder cancer prevention, presumably through inhibition of COX-2. Aberrant expression of COX-2 has been identified in bladder tumours [6] and we have shown that forced expression of COX-2 in premalignant urothelium can contribute to increased cellular growth and a more invasive phenotype [7]. Furthermore, the COX-2-selective inhibitor celecoxib can reduce prostaglandin E_2 levels, inhibit growth, and induce apoptosis in several bladder cancer cell lines, and has been shown to be effective independent of COX-2 expression [8]. The efficacy of COX-2 inhibitors in inhibiting bladder tumour growth was shown in *in vivo* in murine models of bladder cancer. For instance, the nonselective COX inhibitor resveratrol and MF tricyclic, a selective COX-2 inhibitor, was shown to inhibit invasive bladder tumour growth in a p-cresidine-induced murine model of bladder cancer [9]. Furthermore, Grubbs *et al.* [10] showed the growth inhibitory effects of celecoxib on the inhibition of bladder tumour growth by celecoxib in a nitrosamine-induced murine model of bladder cancer. Given these promising data, celecoxib is the focus of a trial for bladder cancer prevention [9].

However, with recent concerns about the risk of cardiovascular toxicity of COX-2-selective inhibitors in terms of cardiovascular risk, COX-2-selective inhibitors have been the focus of much scrutiny, which has led to increased interest in nonselective NSAIDs and COX-independent mechanisms of growth inhibition [8]. Ironically, aspirin as an NSAID, which is a nonselective COX inhibitor, continues to be prescribed as a cardioprotective agent. A significant proportion of patients with bladder cancer have coronary artery disease as another smoking-related illness, and therefore might take aspirin for this purpose. This poses a unique opportunity to evaluate the cancer-preventive potential of an NSAID such as aspirin, which is commonly prescribed in the course of standard care.

Despite many existing epidemiological studies, the relationship of aspirin to the incidence of bladder cancer is not clear. Aspirin has been associated with a lower risk of bladder cancer in a large population-based study of 1514 patients from Southern California [4], and in a smaller study of 376 patients with bladder cancer, in which aspirin was more significant than the use of other NSAIDs [5]. However, low-dose aspirin, given over a 10-year interval as 100 mg every other day, did not lower the incidence of bladder cancer in the Women's Health Study [11]. In the present study of patients undergoing BCG treatment for high-grade noninvasive bladder cancer, we identified a significant relationship between cardioprotective aspirin and a decreased rate of bladder cancer recurrence. This finding is encouraging in terms of a potential role of NSAIDs in bladder chemoprevention, although important limitations of the study should be acknowledged. While this is a single-institution study, which disposes to consistency in practice pattern, this cohort of patients has been evaluated and treated over >10 years, during which practice patterns, such as the indication and schedule for the administration of maintenance BCG, have undoubtedly changed. Furthermore, this is a retrospective study in which available data were obtained from chart review, such that patients lost to follow-up were not evaluable. Finally, the dose of aspirin given could potentially have an effect on efficacy, and the few patients in subset analyses precluded stratification in terms of dose. Nevertheless, these findings are encouraging and support further prospective investigation of the relationship between aspirin and bladder cancer recurrence. While primary prevention studies of agents typically require large numbers of patients followed over relatively long intervals, a multi-institutional study might provide adequate numbers of patients to evaluate over a relatively shorter interval, in which the effects of aspirin and other NSAIDs on tumour recurrence might also be determined.

While preclinical data on NSAIDs would suggest a benefit of aspirin and other nonselective COX inhibitors in terms of tumour progression, we did not identify significantly lower rates of tumour progression in patients taking aspirin. Nevertheless, the mean time to progression was lower in the group taking aspirin (4 vs 3 years). Low event numbers probably precluded an evaluation of this relationship in the present study, whereby a larger prospective study might again be necessary to address this issue.

We also evaluated whether other potentially confounding factors, e.g. current smoking status, administration of BCG and histology (the presence of CIS or papillary tumour) could explain the significant relationship between aspirin and tumour recurrence in this study. Interestingly, aspirin was also a significant factor in the multivariable analysis. Another important point is that most patients in the present study were former smokers, which means that these patients have remained at risk of bladder carcinogenesis despite stopping smoking. However, current smoking status did not confer additional risk compared with former smokers in this analysis. The feasibility of haematuria screening has been reported in the general population, with a significant reduction in the number of deaths due to bladder cancer [12], and as screening continues to be evaluated prospectively, smokers who are at higher risk of developing bladder cancer might benefit from these strategies. Interestingly, the aspirin group was older and still had a significantly reduced recurrence rate, even though BCG is reported to be less effective in the elderly [13]. Finally, maintenance BCG administration was also determined to be a significant factor on multivariable analysis, which might be expected given its known benefit in the Southwest Oncology Group trial [14]. Our findings from the multivariable analysis again suggest a benefit in terms of tumour recurrence in patients taking cardioprotective aspirin.

In conclusion, there was a significantly higher RFS rate in patients taking cardioprotective aspirin after intravesical therapy for bladder cancer. While this study justifies a prospective evaluation of patients, larger prospective multi-institutional studies are probably necessary to determine whether these chemopreventive agents are effective. The results of the present study support the further investigation of aspirin and other NSAIDs as preventive agents in patients being treated for non-muscle-invasive bladder cancer.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **RFS**, recurrence-free survival; **PFS**, progression-free survival; **CIS**, carcinoma *in situ*; **COX**, cyclooxygenase.