Renin-Angiotensin Inhibitors Decrease Recurrence after Transurethral Resection of Bladder Tumor in Patients with Nonmuscle Invasive Bladder Cancer

Michael L. Blute, Jr., Timothy J. Rushmer, Fangfang Shi, Benjamin J. Fuller, E. Jason Abel, David F. Jarrard and Tracy M. Downs*

From the Department of Urology, University of Wisconsin School of Medicine and Public Health, and University of Wisconsin Carbone Comprehensive Cancer Center, Madison, Wisconsin

Abbreviations and Acronyms

ACE-I = angiotensin converting enzyme inhibitor

ARB = angiotensin receptor blocker

AT1 = angiotensin receptor type 1

BCG = bacillus Calmette-Guérin

CIS = carcinoma in situ

NMIBC = nonmuscle invasive bladder cancer

PFS = progression-free survival

RAS = renin-angiotensin system

RFS = recurrence-free survival

TUR = transurethral resection

VEGF = vascular endothelial growth factor

Accepted for publication May 13, 2015.

Study received institutional review board approval.

Supported by T32 Training Grant 5T32CA009614-24 (MLB).

* Correspondence: 1685 University of Wisconsin Medical Foundation Centennial Building, 1685 Highland Ave., Madison, Wisconsin 53792 (telephone: 608-263-9534; FAX: 608-262-6453; e-mail: downs@urology.wisc.edu).

For another article on a related topic see page 1456.

Purpose: Prior reports suggest that renin-angiotensin system inhibition may decrease nonmuscle invasive bladder cancer recurrence. We evaluated whether angiotensin converting enzyme inhibitor or angiotensin receptor blocker treatment at initial surgery was associated with decreased recurrence or progression in patients with nonmuscle invasive bladder cancer.

Materials and Methods: Using an institutional bladder cancer database we identified 340 patients with data available on initial transurethral resection of bladder tumor. Progression was defined as an increase to stage T2. Cox proportional hazards models were used to evaluate associations with recurrence-free and progression-free survival.

Results: Median patient age was 69.6 years. During a median followup of 3 years (IQR 1.3–6.1) 200 patients (59%) had recurrence and 14 (4.1%) had stage progression. Of those patients 143 were receiving angiotensin converting enzyme inhibitor/angiotensin receptor blockers at the time of the first transurethral resection. On univariate analysis factors associated with improved recurrence-free survival included carcinoma in situ ($p = 0.040$), bacillus Calmette-Guérin therapy ($p = 0.003$) and angiotensin converting enzyme inhibitor/angiotensin receptor blocker therapy ($p = 0.009$). Multivariate analysis demonstrated that patients treated with bacillus Calmette-Guérin therapy (HR 0.68, 95% CI 0.47–0.87, $p = 0.002$) or angiotensin converting enzyme inhibitor/angiotensin receptor blocker therapy (HR 0.61, 95% CI 0.45–0.84, $p = 0.005$) were less likely to experience tumor recurrence. The 5-year recurrence-free survival rate was 45.6% for patients treated with angiotensin converting enzyme inhibitor/angiotensin receptor blockers and 28.1% in those not treated with angiotensin converting enzyme inhibitor/angiotensin receptor blockers ($p = 0.009$). Subgroup analysis was performed to evaluate nonmuscle invasive bladder cancer pathology (Ta, T1 and carcinoma in situ) in 85 patients on bacillus Calmette-Guérin therapy alone and in 52 in whom it was combined with angiotensin converting enzyme inhibitor/angiotensin receptor blocker. Multivariate analysis revealed that patients treated with bacillus Calmette-Guérin alone (HR 2.19, 95% CI 1.01–4.77, $p = 0.04$) showed worse recurrence-free survival compared to patients treated with bacillus Calmette-Guérin and angiotensin converting enzyme inhibitor/angiotensin receptor blocker (stage Ta HR 0.45, 95% CI 0.21–0.98, $p = 0.04$).

Conclusions: Pharmacological inhibition of the renin-angiotensin system is associated with improved outcomes in patients with bladder cancer. Renin-angiotensin system inhibitor administration in nonmuscle invasive bladder cancer cases should be studied in a prospective randomized trial.

0022-5347/15/1945-1214/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2015.05.104
Vol. 194, 1214-1219, November 2015
Printed in U.S.A.

Key Words: urinary bladder neoplasms; neoplasm recurrence, local; renin-angiotensin system; angiotensin converting enzyme inhibitors; angiotensin receptor antagonists

LIKE most genitourinary cancers, transitional cell cancer relies on proangiogenic factors for growth and metastasis.[1] Yet despite this knowledge many currently available intravesical therapies for NMIBC disregard this potential avenue of treatment. Most diagnosed bladder cancers are NMIBC and the most commonly reported pathological finding is stage Ta following TUR.[2] Standard treatment of NMIBC after TUR includes intravesical instillation of chemotherapy or BCG immunotherapy.[3] Despite its proven success in decreasing bladder cancer recurrence BCG failure remains a distinct possibility following an initial response according to long-term data.[4] Cookson et al randomized 86 patients to TUR for NMIBC with or without BCG.[4] The 15-year followup data revealed no significant difference in PFS rates (53%). BCG and intravesical therapies are pivotal for long-term treatment of NMIBC. However, the results of that study and others[5] highlight the need to generate new treatment options for NMIBC that can be used alone or in conjunction with BCG.

While AT1 receptor expression has been demonstrated in bladder cancer, a recent report outlined the effect of RAS blockade on RFS.[6] RAS blockade with ACE-Is or ARBs delayed time to recurrence in patients with NMIBC (Ta, T1 and CIS). This effect was seen when the medications were administered alone or in combination with BCG therapy. Therefore, we sought to validate in our data set whether inhibiting RAS with ACE-Is and ARBs would provide a clinical benefit on recurrence and progression of NMIBC.

MATERIALS AND METHODS

We reviewed our institutional NMIBC database at University of Wisconsin and identified 421 patients from 1998 to 2014. All patients were identified as having NMIBC following TUR. Patients were excluded from analysis if they had no medication history, and if they were not on RAS blockade at the time of the first TUR. After excluding 81 patients who did not meet inclusion criteria 340 were available for analysis.

Tumor recurrence was identified on subsequent TUR and confirmed after pathological review. Stage progression was defined as evidence of tumor invasion of the muscularis propria on followup TUR. CIS was defined as histologically confirmed CIS in the presence or absence of Ta/T1 tumors as defined by the EORTC (European Organisation for Research and Treatment of Cancer). Independent variables assessed included patient age; gender; diabetes mellitus type II; smoking status; tumor grade, stage and multiplicity; CIS; BCG; and intravesical therapy. Medication history, ie use of ACE-I/ARBs, was obtained from electronic medical records according to the patient medical records.

Univariate and multivariate Cox proportional hazard regression models with backward selection were used to analyze associations of variables with tumor recurrence and progression. RFS and PFS curves were generated by the Kaplan-Meier method and compared with the log rank test. Variables at $p < 0.05$ were considered significant. Statistical analysis was done using SAS®, version 9.2.

RESULTS

We reviewed our institutional NMIBC database and identified 421 patients, of whom 340 met study inclusion criteria. Patients identified as having received ACE-I/ARBs were only included if they were on the medications at the time of the first TUR. Table 1 lists clinical and pathological characteristics

Table 1. *Clinical and pathological characteristics of patients by ACE-I/ARB administration*

	No. ACE-I/ARB (%)		
	No	Yes	p Value
Age:			0.006
Less than 65	87 (44.2)	42 (29.4)	
Greater than 65	110 (55.8)	101 (70.6)	
Gender:			0.76
M	153 (77.7)	113 (79)	
F	44 (22.3)	30 (21)	
Smoking:			0.4
Current	37 (18.9)	21 (14.7)	
Former	104 (53.1)	86 (60.1)	
Never	55 (28.1)	36 (25.2)	
Multifocality:			0.67
Yes	80 (41)	62 (43.4)	
No	115 (59)	81 (56.6)	
Intravesical chemotherapy:			0.11
Yes	32 (16.2)	33 (23.1)	
No	165 (3.8)	110 (76.9)	
BCG therapy:			0.21
Yes	85 (43.1)	52 (36.4)	
No	112 (56.9)	91 (63.3)	
Stage:			0.05
Ta	130 (66)	99 (69.2)	
T1	44 (22.3)	38 (26.6)	
CIS	23 (11.7)	6 (4.2)	
Grade:			0.51
Low	88 (47.7)	69 (48.3)	
High	109 (55.3)	74 (51.7)	
Tumor size (cm):			0.73
Less than 3	115 (61.2)	87 (63)	
Greater than 3	73 (38.8)	51 (37)	
Muscle in specimen:			0.48
No	134 (68)	92 (64.3)	
Yes	63 (32)	51 (35.7)	
Second TUR:			0.08
No	179 (90)	121 (84.6)	
Yes	18 (9.1)	22 (15.4)	
Mitomycin C:			0.01
No	180 (91.4)	117 (81.8)	
Yes	17 (8.6)	26 (18.2)	