Bladder Cancer 2 (2016) 123–125
DOI 10.3233/BLC-169001
IOS Press

Paper Alert

Edward M. Messing*
University of Rochester Medical Center, Rochester, USA

Bladder cancer (BC) occurs roughly 3 times as often in men as women, not only in the United States, but worldwide [1]. This ratio has changed little over the past 30 years despite women entering the male workplace and increasing their relative exposure to bladder carcinogens such as those in cigarette smoke.

One explanation for the gender disparity in BC incidence is differences in sex hormone status and sex hormone receptor activity – particularly the androgen receptor (AR) [2–6]. Over the past several months, five articles have appeared which confirm this relationship, particularly studying the influence of anti-AR therapies on the development of BC and preventing its recurrence. Two of these studies have investigated the molecular mechanisms by which the AR achieves its BC stimulating effect and how the AR may promote refractoriness to an important BC treatment, intravesical instillations of Bacillus Calmette-Guerin (BCG). Each study points to a promising AR inhibiting approach to prevent BC development or recurrence.

Studying the Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial database, Morales and colleagues reported on the risk of developing BC in 72,370 male participants over the 4 years of screening and a 13 year follow up period [7]. Men who self-reported taking the 5 alpha reductase inhibitor (5ARI), finasteride for >1 year during the study ($N = 6069$) had a significantly lower incidence of developing BC during the 4 year trial (1.07%) than the 66,301 who did not take this or similar medicines (1.46%) (HR 0.634, 95% CI 0.493 – 0.816; $p = 0.0004$). This effect continued over the 13 year follow-up (finasteride 1.3% vs 1.8% no 5 ARI's, $p = 0.002$). The findings presented were controlled for age and smoking status. However there was no significant effect on BC mortality and indeed the risk reduction was primarily for grade 1 and 2 urothelial BCs, and not grade 3 BC.

*Correspondence to: Edward M. Messing, University of Rochester Medical Center, Rochester, USA. E-mail: Edward_messing@urmc.rochester.edu.

The authors appropriately point out limitations of the study including the possible lack of reliability of self-reporting finasteride use, and that while prospective, this was not a randomized trial – in terms of risks for developing BC. However, this is a thoroughly followed cohort with careful reporting of medications, risk factors and bladder cancer diagnoses, whose accuracy could not be matched in most large administrative databases.

Looking at the effects of androgen deprivation therapy (ADT) and other treatments for 1334 Japanese men undergoing primary treatment for prostate cancer, despite having higher grades and stages of prostate cancer (most had nodal and/or distant metastases) and more advanced age, men receiving castrative therapies had a significantly lower instance of subsequently being diagnosed with BC over a 4-5 year median follow up, than men receiving external beam radiation (EBRT), prostate brachytherapy, EBRT + prostate brachytherapy, or radical prostatectomy (open or robotic). Indeed none of the 266 men receiving primary ADT developed BC compared with 1.1% of men undergoing prostatectomy and 2.2% of those receiving various forms of radiation (5.2% receiving primary EBRT). These effects continued over 10 years of follow up. While an increased incidence of BC in men treated with EBRT has been reported before [8–13], this is the first report of a reduced incidence in men receiving ADT alone.

In a separate study by Izumi et al. [14] the incidence of BC recurrences in men receiving ADT for prostate cancer was evaluated and correlated with immunohistochemically detected AR expression in tumors. 44 of 72 (61%) NMI BCs expressed ARs (defined as >10% of tumor cells expressing AR or >1% showing moderate or strong staining). Although AR expression did not correlate with tumor grade or stage, in patients receiving ADT, men with AR expressing BCs had a significantly lower chance of recurring (11/44 [23%] over 5 years) than did those with AR negative tumors

ISSN 2352-3727/16/€27.50/$35.00

(12 of 28 recurred [43%]) $p = 0.031$. AR expression in nonmalignant urothelium and estrogen receptor (ER) alpha and beta expression (in malignant or normal urothelium) did not correlate with BC recurrence. The conclusion was that AR positive tumors were more likely to be dependent on AR signals than AR negative tumors. Hence, when ligand was depleted (by ADT) and the ARs relatively silenced, the BCs expressing ARs were more likely to be suppressed than those that were AR negative; thus, the former would recur less often. AR negative and AR positive BCs were relatively similar in grade, stage, size, multiplicity and treatment with intravesical chemotherapy or BCG. These factors and the means of ADT, LHRH agonist with or without antiandrogens, did not influence the effects of AR expression on recurrence.

Besides its small sample size, there are other limitations to this study including its retrospective design, failure to measure androgen levels, lack of quantification of AR expression (beyond binary positive and negative) and analysis of its influences on recurrence, not reporting whether index tumors were newly diagnosed or recurrent or whether prior EBRT had been administered, and how overall AR status was assigned when there were multiple tumors which differed in AR positivity. Despite these factors, however, this work certainly supports the concept that the AR is important in BC development and recurrence.

And what are some of the key AR molecular signals influencing BC behavior?

Kawahara, et al. [15] found that in human BC cells, ELK1, a transcription factor which activates downstream targets including the c-fos proto-oncogene, is an important mediator of AR activity. In clinical tissue samples, the intensity of phosphorylated ELK 1 (pELK1) expression in nuclei of BC cells correlated with recurrence of NMI BC, and with disease progression and cancer mortality in muscle invasive (MI) BC, as well as with AR expression. In androgen responsive BC cell lines, ELK1 knockdown inhibited androgen stimulation of mitosis, migration, invasion, and subcutaneous growth in nude mice. Activated AR stimulates ELK1 activity not only by increasing ELK1 expression but also by stimulating it's phosphorylation. Antiandrogens inhibit this effect.

While these experiments were only performed in a few cell lines, this mechanism also appears to be important in other tumors (e.g. androgen dependent prostate cancer cells) and lends molecular support for using anti-AR therapies in BC.

Anti-AR therapy may not only directly inhibit BC growth, but can influence one of the primary therapies against BC, intravesical instillations of BCG. Using both AR positive human BC cell lines and the BBN induced mouse BC model, Shang, et al. [16] found that both *in vitro* and *in vivo* treatment with the antiandrogen, hydroxyflutamide (HF) or the enhancer of AR degradation, ASCJ9, augmented BCG's anti-BC effects, at least in part by enhancing alpha 5-beta 1 integrin expression so that BCG attachment and internalization were improved. HF and ASCJ9 also stimulated the cytokine release of Il-6, a monocyte and macrophage attractant, by the BCG-infected BC cells. The inflammatory infiltrate also increased TNF alpha secretion by BCG-recruited macrophages and monocytes, enhancing BCG's killing of BC cells. BCG's direct lethality to infected BC cells, by inducing host cells to secrete high-mobility group box 1 (HMGB1), is also increased with HF or ASCJ9. Thus, through several mechanisms, BCG's effects on BC are increased with AR inhibition. This was confirmed with *in vivo* studies.

While utilizing only 2 BC cell lines and 1 *in vivo* carcinogen induced BC model, antiandrogen activity has been shown to increase BCG's anti BC activity.

These 5 studies use similar approaches to prevent BC from developing and recurring, strongly supporting a role for AR inhibition in attacking this disease. It appears it's time for this strategy to be tested in clinical trials.

REFERENCES

[1] Donsky H, Coyle S, Scosyrev E, et al. Sex differences in incidence and mortality of bladder and kidney cancers: National estimates from 49 countries. Urol Oncol. 2014;32(1):40.

[2] Miyamoto H, Yang Z, Chen Y-T, et al. Promotion of bladder cancer development and progression by androgen receptor signals. JNCI 2007;99:558-68.

[3] Johnson AM, O'Connell MJ, Miyamoto H, et al. Androgen dependence of exophytic tumor growth in a transgenic mouse model of bladder cancer: A role for thrombospondin-1. BMC Urol 2008;8:7.

[4] Zheng Y, Izumi K, Yao JL, et al. Dihydroteststerone upregulates the expression of epidermal growth factor receptor and ERBB2 in androgen receptor-positive bladder cancer cells. Endocr Relat Cancer 2011;18:451-464.

[5] Li Y, Izumi K, Miyamoto H. The role of the androgen receptor in the development and progression of bladder cancer. Jpn J Clin Oncol 2012;42:569-77.

[6] Izumi K, Taguri M, Miyamoto H, et al. Androgen deprivation therapy prevents bladder cancer recurrence. Oncotarget 2014;5:12665-74.

[7] Morales E, Grill S, Svatek R, et al. Finasteride reduces risk of bladder cancer in a large prospective screening study. Eur Urol, 2015 in press.

[8] Bostrom PH, Soloway MS. Secondary cancer after radiotherapy for prostate cancer: Should we be more aware of the risk? Eur Urol 2007;52:973-82.

[9] Neugut AL, Ahsan H, Robinson E, et al. Bladder carcinoma and other second malignancies after radiotherapy for prostate carcinoma. Cancer 1997;79:1600-4.
[10] Brenner DJ, Curtis RE, Hall EJ, et al. Second malignancies in prostate carcinoma patients after radiotherapy for prostate cancer. Cancer 2000;88:398-406.
[11] Moon K, Stukenborg GJ, Keim J, et al. Cancer incidence after localized therapy for prostate cancer. Cancer 2006;107:991-8.
[12] Abdel-Wahab M, Reis IM, Hamilton K. Second primary cancer after radiotherapy for prostate cancer – a SEER analysis of brachytherapy versus external beam radiation. Int J Radiat Oncol Biol Phys 2008;72:58-68.
[13] Nieder AM, Porter MP, Soloway MS. Radiation therapy for prostate cancer increases subsequent risk of bladder and rectal cancer: A population based cohort study. J Urol 2008;180:2005-9.
[14] Izumi K, Ito Y, Miyamoto H, et al. Expression of androgen receptor in non-muscle invasive bladder cancer predicts the preventive effect of androgen deprivation therapy on tumor recurrence. Oncotarget, 2015, in press.
[15] Kawahara T, Shareef HK, Aljarah AK, et al. ELK1 is up-regulated by androgen in bladder cancer cells and promotes tumor progression. Oncotarget, Advanced Pub, 2015.
[16] Shang Z, Li Y, Zhang M, et al. Antiandrogen therapy with hydroxyflutamide or androgen receptor degradation enhancer ASC-J9 enhances BCG efficacy to better suppress bladder cancer progression. Mol Cancer Ther, in press, 2015 AACR.