Bladder Cancer Survival in Men Receiving 5α-Reductase Inhibitors

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Purpose: Androgens may have a role in bladder carcinogenesis. We studied whether 5α-reductase inhibitors were associated with bladder cancer specific mortality in a population based cohort of men with bladder cancer.

Materials and Methods: The study cohort consisted of 10,720 Finnish men with bladder cancer newly diagnosed in 1997 to 2012 who were identified in a national cancer registry. Median followup was 4.17 years after bladder cancer diagnosis. We analyzed the HR and 95% CI of the risk of bladder cancer death by 5α-reductase inhibitor administration using Cox regression adjusted for age, gender, comorbidities, primary bladder cancer treatment and tumor extent at diagnosis. Lag time analyses were performed to assess the long-term risk association. Simultaneous administration α-blockers was considered to estimate possible confounding by indication.

Results: Administering 5α-reductase inhibitors before bladder cancer diagnosis was associated with a lower risk of bladder cancer death (HR 0.84, 95% CI 0.73–0.97). The risk decrease became stronger with years of use. Conversely prediagnostic administration of α-blockers was not associated with bladder cancer survival (HR 1.02, 95% CI 0.91–1.13). Similarly 5α-reductase inhibitor administration after diagnosis was associated with a decreased risk of bladder cancer death (HR 0.77, 95% CI 0.68–0.88). Bladder cancer survival was not associated with α-blockers (HR 0.98, 95% CI 0.90–1.07). The risk decrease due to 5α-reductase inhibitors persisted up to 5 years.

Conclusions: Patients who receive 5α-reductase inhibitors have improved disease specific survival after bladder cancer diagnosis compared to those who do not receive them while α-blockers were not associated with survival. This supports the benefits of 5α-reductase inhibitors in bladder cancer.

Key Words: bladder neoplasms, 5-alpha reductase inhibitors, Finland, survival, adrenergic alpha-antagonists

Abbreviations and Acronyms

5-ARI = 5α-reductase inhibitor

BCa = bladder cancer

HILMO = Care Register for Health Care

TURB = transurethral resection of bladder

SII = Social Insurance Institution of Finland

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Urothelial bladder cancer is the sixth most common cancer type among men worldwide.[1] More than 70% to 80% of bladder cancers are superficial and treatable with TURB, often combined with intravesical instillation. In 25% of cases bladder cancer infiltrates the muscle layer of the bladder wall. In these cases radical cystectomy combined with chemotherapy is often needed. Fewer than 10% of bladder cancers have already metastasized by diagnosis and they are palliatively treated with chemotherapy and radiation. Tumors are also classified by cytology into low

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or high grade with high grade the most malignant and potentially invasive type.[2]

Superficial low grade bladder cancer often recurs but disease specific survival is excellent. This is not the case for muscle infiltrating invasive cancer, which has a 5-year survival rate of 50% to 65%. Metastatic disease is still incurable and life expectancy is less than 16 months.[3]

The prevalence of bladder cancer is higher in men than in women. To our knowledge the reason for the gender difference is unknown but androgens were proposed to have an impact on urothelial carcinogenesis and androgen receptor signaling may promote the growth of urothelial cancer cells.[4] The importance of androgens in urothelial bladder cancer was supported by a recent study showing a reduced incidence of bladder cancer in men who received the 5-ARI finasteride or dutasteride compared to nonusers.[5] These drugs inhibit conversion of testosterone to dihydrotestosterone, a more potent activator of androgen signaling.

The enzyme 5α-reductase is expressed mainly in the prostate and 5-ARIs are mainly used to manage benign prostatic hyperplasia. However, 5α-reductase is also expressed by urothelial cancer cells and dihydrotestosterone affects the growth of those cells.[6,7] Therefore, it can be presumed that 5-ARIs would benefit patients with bladder cancer. However, currently to our knowledge no published studies have described how 5-ARIs may affect the bladder cancer prognosis.

We performed a population based cohort study in Finland to estimate whether 5-ARI use is associated with bladder cancer prognosis. Our hypothesis was that the prognosis would be better among men who received 5-ARI. As 5-ARIs are used to treat benign prostate hyperplasia and lower urinary tract symptoms caused by benign prostate hyperplasia, 5-ARI users are more likely than nonusers to be under urologist supervision, creating possible selection bias. To assess and control for this bias we additionally analyzed the risk association with α-blockers, which are used partly for the same indications.

MATERIALS AND METHODS

Study Population

We collected the records of all urothelial cancers of the bladder diagnosed in Finland during 1997 to 2012 from the comprehensive national FCR (Finnish Cancer Registry) based on ICD-10 codes (C67.0-C67.9).[8] A total of 10,720 men were included in study. Available data included date of cancer diagnosis, tumor extent (localized, locally advanced or metastatic), primary treatment (surgery vs other), and the date and the cause of death. The FCR data were linked to the HILMO information based on personal unique identification numbers. HILMO data contained diagnoses and procedures recorded at hospital contacts at Finnish health care units in 1997 to 2012.[9] The HILMO data were used to evaluate comorbidities (diabetes, hypercholesterolemia and hypertension) and obtain information on the timing and the number of endoscopic and open surgical procedures for bladder cancer after diagnosis. Surgical procedures were identified by procedure codes KCD02, KCD05, KCD32, KCC00, KCC10 and KCC20 (supplementary Appendix, http://jurology.com/).

Medication Information

The study cohort was linked to the national prescription database managed by the SII to obtain data on 5-ARI (finasteride and dutasteride) medication purchases in 1997 to 2012. Additionally, data on cholesterol lowering, antihypertensive and antidiabetic drug purchases were also collected. The database provided detailed information on each medication purchase, including the date of purchase, ATC (Anatomical Therapeutic Chemical) code, package size and dose.

As part of the national health insurance available to all Finnish citizens, SII partly covers costs of physician prescribed drug purchases.[10] The reimbursement is available to all Finnish citizens. Each reimbursed prescription purchase is recorded regardless of the rate of SII cost coverage. Because in Finland α-blockers and 5-ARIs are available only by prescription, they are comprehensively recorded by the database. The only exception is 1 mg finasteride used to treat androgenetic alopecia. Over-the-counter medications and medications used during inpatient are also not recorded by the database.

Statistical Analysis

Age distribution, tumor and treatment characteristics, and the prevalence of comorbidities were compared by 5-ARI use before and after the bladder cancer diagnosis. We applied the chi-square test to test for statistical significance of differences in categorical variables and the Mann-Whitney U-test for noncategorical variables. Analyses of prediagnostic and post-diagnostic use were done in separate models.

Logistic regression was used to calculate the OR and 95% CI of the risk of more than 2 or more than 5 TURBs after bladder cancer diagnosis. The logistic regression model was adjusted for age and comorbidities.

We analyzed the HR and 95% CI of the risk of bladder cancer death using Cox regression adjusted for age, gender, comorbidities, primary bladder cancer treatment (surgery vs other) and tumor extent at diagnosis (localized vs metastatic). Unknown tumor extent was included in analysis as 1 category. The time metric was years and months since bladder cancer diagnosis. Followup continued until death, emigration or the common closing date of December 31, 2012, whichever was first.

Medication use was divided into prediagnostic and post-diagnostic administration according to the year of drug purchases. Use at the year of diagnosis was included in post-diagnostic use. Patients who received 5-ARIs were stratified into 2 subgroups by the median number of 5-ARI doses per year. Similar stratifications were done for α-blockers.