Association of Itraconazole, a Hedgehog Inhibitor, and Bladder Cancer

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Purpose: Activation of Hedgehog (Hh) signaling has been implicated in early stages of bladder cancer development while loss of Hh signaling has been described during progression to more invasive disease. Itraconazole, an antifungal, is the only azole known to be a potent Hh pathway antagonist. We evaluated whether itraconazole use is associated with bladder cancer risk or progression.

Materials and Methods: We performed a case-control study nested in a United Kingdom database in 13,440 bladder cancer cases and 52,421 matched controls between 1995 and 2013. The use of itraconazole and other azoles was measured as the number of prescriptions. Conditional logistic regression was used for estimated AORs and the 95% CI of the association of bladder cancer with ever use and an increasing number of itraconazole prescriptions. Logistic regression was done to determine whether itraconazole use in patients diagnosed with bladder cancer was associated with invasive bladder cancer requiring cystectomy relative to the use of other azoles.

Results: Itraconazole was not associated with the risk of bladder cancer relative to never use (ever use AOR 0.89, 95% CI 0.70–1.14 and 4 or more prescriptions AOR 0.87, 95% CI 0.42–1.81). However, among patients diagnosed with bladder cancer there was a significantly increased risk of bladder cancer requiring cystectomy with itraconazole use (ever use AOR 2.05, 95% CI 1.12–3.38 and 2 or more prescriptions AOR 2.30, 95% CI 1.12–4.72).

Conclusions: Inhibition of the Hh pathway with itraconazole was not associated with a risk of bladder cancer overall but it was associated with a higher risk of invasive bladder cancer requiring cystectomy. These data provide clinical evidence supporting the role of Hh signaling in regulating bladder cancer progression.

Key Words: urinary bladder neoplasms, itraconazole, antifungal agents, risk, cystectomy

Abbreviations and Acronyms

THIN = The Health Improvement Network

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THE Hh signaling pathway is a developmental pathway that has an important role in human embryogenesis.[1] Constitutive activation of this pathway has been implicated in oncogenesis, particularly bladder carcinogenesis.[2] Carcinoma of the bladder, which arises from the uroepithelium, is the ninth most common cancer worldwide with a global prevalence of 2.7 million cases.[3] Recently, Hh expressing urothelial basal stem

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cells have been identified as the cell of origin in bladder carcinoma.[4] While Hh expression promotes epithelial proliferation early in bladder cancer development, loss of expression has been associated with progression into invasive disease.[5] Therefore, inhibition of the Hh signaling pathway could have differential effects on bladder cancer risk or progression.

Itraconazole, a currently available oral antifungal agent, is a potent Hh pathway antagonist via a mechanism separate from the inhibition of the fungal mediated synthesis of ergosterol.[6] Itraconazole has also been suggested to inhibit angiogenesis in tumor cells.[7] To our knowledge there are no available data on the effect of itraconazole exposure on the risk or progression of bladder cancer.

Given that other drugs in the azole class are not inhibitors of the Hh pathway, we examined the risk of bladder cancer in users of itraconazole and other azoles. We also examined whether itraconazole use in patients diagnosed with bladder cancer is associated with more invasive bladder cancer requiring cystectomy.

MATERIALS AND METHODS

Data Source

THIN (http://www.epic-uk.org/our-data/our-data.shtml) is a computerized medical record database representative of the broader United Kingdom. The database currently contains the electronic records of more than 11 million patients. Data available in THIN include demographic information, medical diagnoses, drug prescriptions, lifestyle characteristics such as smoking status and other measurements recorded by general practitioners such as height and weight. Medical diagnoses entered into the database are recorded using Read codes, which is the standard primary care classification system in the United Kingdom.[8] Data quality is monitored by routine analysis of the entered data.[9] The accuracy and completeness of THIN data are well documented[10,11] and the database has been previously used to study the pharmacoepidemiology of bladder cancer.[12,13]

Study Design and Population

We performed a nested case-control analysis in THIN. The case-control design is computationally efficient and produces ORs that are unbiased estimates of incidence rate ratios.[14] All patients registered with a THIN general practitioner from 1995 to 2013 were eligible for study inclusion. Followup started at the later of the date that the THIN practice started using the electronic medical record (Vision, INPS, London, United Kingdom) or the date at which the patient registered with the general practitioner. Followup ended on the index date as described. The study protocol was approved by the University of Pennsylvania institutional review board and the United Kingdom scientific review committee.

Case-Control Selection

In the source cohort cases were defined as individuals with at least 1 diagnostic code for bladder cancer during followup (supplementary Appendix, http://jurology.com/).[15] Subjects with a diagnosis of bladder cancer within the first 6 months of followup were excluded from analysis to avoid misclassifying prevalent bladder cancer as incident bladder cancer.[11,16] Selection of controls was based on incidence density sampling.[17] For each individual with bladder cancer up to 4 controls were randomly selected after matching by age ($\pm$ 5 years), gender, practice site, followup duration and calendar period. Additionally, each control could not have been diagnosed with bladder cancer as of the date of the bladder cancer diagnosis of the matched case subject. The date that the case subject was first diagnosed with bladder cancer served as the index date for the case subject and for the matched control.

Exposure Definition

Exposure to itraconazole was defined as receipt of at least 1 oral prescription for itraconazole at least 1 year before the index date. Identical definitions were used to define exposure to other azoles (fluconazole, miconazole, ketoconazole and voriconazole). We did not consider any azole use in the year immediately prior to the index date to minimize the possibility that azoles were prescribed due to nonspecific symptoms of undiagnosed bladder cancer (reverse causality).

Statistical Analysis

Conditional logistic regression was used to calculate the ORs and 95% CIs for the association of itraconazole use and bladder cancer risk adjusted for confounders.[18] The reference group in this analysis consisted of subjects without documented use of azole antifungal medication before the index date. In addition to age, gender, practice site, followup duration and calendar period, on which logistic regression analyses were conditioned, we included 7 factors a priori as confounding variables. These 7 variables were smoking, obesity (body mass index 30 kg/m^2 or greater), diabetes mellitus, use of diabetes medication (metformin, insulin or thiazolidinediones), chronic use of aspirin or nonsteroidal anti-inflammatory medication and recurrent bladder infections, given the association of these variables with the risk or detection of bladder cancer.

We also examined the risk of bladder cancer with increasing exposure to itraconazole. We measured exposure in terms of the number of itraconazole prescriptions starting with the first prescription that defined ever use of itraconazole. The reference group for this analysis was never use of itraconazole. Similar analyses were performed to examine the risk of bladder cancer with the use of other azole antifungal medications.

On analysis limited to users of any azole we examined the association of bladder cancer with itraconazole treatment relative to treatment with other azole antifungals. Due to the fewer number of cases exposed to an azole in this subset analysis unconditional logistic regression was used, adjusted for age, gender, calendar time and followup duration as well as the prespecified set of confounders.