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Prostate Cancer

Gonadotropin-releasing Hormone Agonists and Acute Kidney Injury in Patients with Prostate Cancer

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Abstract

Background: Androgen deprivation therapy (ADT) might increase the risk of acute kidney injury (AKI) in patients with prostate cancer (PCa).
Objective: To examine the impact of ADT on AKI in a large contemporary cohort of patients with nonmetastatic PCa representing the US population.
Design, setting, and participants: Overall, 69 292 patients diagnosed with nonmetastatic PCa between 1995 and 2009 were abstracted from the Surveillance Epidemiology and End Results–Medicare database.
Outcomes measurements and statistical analyses: Patient in both treatment arms (ADT vs no ADT) were matched using propensity-score methodology. Ten-year AKI rates were estimated. Competing-risks regression analyses tested the association between ADT and AKI, after adjusting for the risk of death during follow-up.
Results and limitations: Overall, the 10-yr AKI rates were 24.9% versus 30.7% for ADT-naive patients versus those treated with ADT, respectively ($p < 0.001$). When patients were stratified according to the type of ADT, the 10-yr AKI rates were 31.1% versus 26.0% for men treated with gonadotropin-releasing hormone (GnRH) agonists and bilateral orchiectomy, respectively ($p < 0.001$). In multivariable analyses, the administration of GnRH agonists (hazard ratio [HR]: 1.24; 95% confidence interval [CI], 1.18–1.31; $p < 0.001$), but not bilateral orchiectomy (HR: 1.11; 95% CI, 0.96–1.29; $p = 0.1$), was associated with the risk of experiencing AKI. Our study is limited by its retrospective design.
Conclusions: ADT is associated with an increased risk of AKI in patients with nonmetastatic PCa. In particular, the administration of GnRH agonists, but not surgical castration, may substantially increase the risk of experiencing AKI. These observations should help provide physicians with better patient selection to reduce the risk of AKI.
Patient summary: The administration of gonadotropin-releasing hormone agonists, but not bilateral orchiectomy, increases the risk of acute kidney injury (AKI) in patients with prostate cancer (PCa). These observations should help provide physicians with better patient selection to reduce the risk of AKI in PCa patients.

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1. Introduction

In 1941, Huggins and Hodges for the first time noted the beneficial effects of androgen deprivation in patients with metastatic prostate cancer (PCa) [1]. Since then, both medical and surgical androgen deprivation therapies (ADT) have become a widely adopted therapeutic approach for patients with clinically localized or metastatic disease [2,3].

Although ADT has been shown to improve oncologic outcomes [2], its administration is associated with a non-negligible risk of important side effects [2,4,5]. A report by Lapi et al. [6] showed that ADT might also have a detrimental impact on renal function. Based on a nested case-control study within an observational cohort, the authors found that ADT was associated with a meaningful risk of experiencing hospitalization for acute kidney injury (AKI) [6]. In spite of the well-designed nature of the study, this report represents the first evidence of the association between ADT and AKI in PCa patients. Moreover, the data originated from men diagnosed and treated in the United Kingdom. Consequently, they require validation in other settings and pertinent populations prior to warranting a challenge in clinical practice. We aimed to examine the impact of ADT on the risk of AKI in a large contemporary population-based cohort representative of the United States.

2. Materials and methods

2.1. Population source

The current study relied on the most recent version of the Surveillance Epidemiology and End Results (SEER)–Medicare insurance program linked database. This database is 98% complete for case ascertainment. The SEER registries cover approximately 28% of the US population with Medicare administrative data. Medicare insurance includes approximately 97% of Americans ≥65 yr of age.

2.2. Study population

Overall, 234 198 patients with histologically confirmed nonmetastatic PCa (International Classification of Disease (ICD) for Oncology site code 61.9, histologic code 8140) ≥66 yr of age diagnosed between January 1995 and December 2009 were identified. To limit the potential selection biases related to the administration of curative-intent treatments, we considered only patients who did not receive any active treatment (ie, radical prostatectomy, radiotherapy, and brachytherapy) during the first 12 mo after diagnosis. This resulted in 94 705 individuals. Exclusion criteria consisted of patients with baseline chronic kidney failure (CKF), AKI, or receiving dialysis treatment ($n = 7951$), unknown socioeconomic status ($n = 4511$), unknown stage ($n = 6374$), and unknown Gleason score ($n = 6579$). This resulted in a final population of 69 292 assessable patients.

2.3. Covariates

The use of ADT after diagnosis was assessed according to previously described methodologies [7]. Patients were divided in two groups according to the exposure to ADT during follow-up: ADT versus ADT naive. Data on the type of ADT (gonadotropin-releasing hormone [GnRH] agonist administration or bilateral orchiectomy) were also abstracted. For each patient, age at diagnosis, year of diagnosis, race, population density, marital status, region, education, income, Gleason score, and clinical stage were assigned [8]. The Charlson Comorbidity Index (CCI) was derived from the Medicare claims 1 yr prior to PCa diagnosis [9].

2.4. Outcomes

The outcome of interest was the occurrence of AKI. This was identified using diagnostic and therapeutic codes for acute renal failure and dialysis (Supplemental Table 1). In patients exposed to ADT during follow-up, time to AKI was calculated from the date of ADT initiation to the first occurrence of AKI. In patients who were not exposed to ADT during follow-up, time to AKI was calculated from the date of diagnosis to the first occurrence of AKI.

2.5. Statistical analyses

Our statistical analyses consisted of three main steps. First, due to inherent differences between patients undergoing ADT and ADT-naive individuals, adjustment was performed using 0.5–0.5 propensity-score matching. When matching is performed, the covariates of the control and treatment groups are balanced to reduce possible biases to a minimum [10]. Propensity scores were computed by modeling a logistic regression with the dependent variable as the odds of receiving ADT, and the independent variable as age, year, CCI, race, population density, marital status, region, education, income, Gleason score, and clinical stage. Subsequently, covariate balances between the matched groups were examined [11]. Second, cumulative incidences of AKI were generated for different treatment groups and compared with the Gray test [12]. In addition, to evaluate and illustrate the risk of AKI associated with ADT, we derived the number needed to harm (NNH), defined as the number of patients who must be treated to encounter one harmful outcome of interest. Finally, competing-risks regression models for the prediction of AKI were fitted. In particular, we examined the effect of ADT after accounting for the competing event of any death, as well as the previously mentioned variables.

All statistical tests were performed using the R statistical package (v.2.15.2). All tests were two sided with a significance level set at $p < 0.05$. Our study was approved by the University of Montreal Health Center; patient data were unidentified, and the requirement for consent was waived.

2.6. Sensitivity analyses

We conducted four sensitivity analyses to assess the robustness of our findings. First, we adjusted our multivariable regression models for comorbidities associated with the risk of AKI (namely, cardiovascular comorbidities, hypertension, diabetes mellitus, alcohol abuse, and obesity; Supplemental Table 2) [6]. Second, we repeated our analyses after adjusting for the use of bisphosphonate, which has been shown to increase the risk of kidney failure [13]. Third, to minimize the potential bias related to the presence of postrenal AKI in patients who experienced obstruction due to local progression, separate subanalyses were performed, where patients who underwent nephrostomy, pyelostomy, ureterotomy, and cystourethroscopy with ureteral catheterization were excluded ($n = 1618$). Finally, we performed separated analyses assessing the association between ADT and the risk of CKF.

3. Results

3.1. Baseline characteristics

Table 1 depicts the baseline characteristics of patients included in the study. Respectively, 37 755 (54.5%) were

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