Prostate Cancer and Prostatic Diseases (2021) 24:933–934
https://doi.org/10.1038/s41391-021-00383-8

EDITORIAL

Androgen deprivation therapy and acute kidney injury in prostate cancer: room for debate?

Timothy J. Daskivich[1]

Received: 12 March 2021 / Revised: 22 April 2021 / Accepted: 28 April 2021 / Published online: 18 May 2021

Androgen deprivation therapy (ADT) remains widely used in the treatment of prostate cancer at various timepoints in the disease course. It is the standard of care for treatment of men with metastatic prostate cancer [1], for adjuvant treatment with radiotherapy for men with high metastatic risk [2], and is frequently used for biochemical recurrence after definitive treatment [3]. While ADT has been shown to improve quality of life and reduce morbidity [4], it carries substantial risks of constitutional, musculoskeletal, cognitive, and cardiometabolic side effects [5]. ADT causes fatigue, decreased libido, and hot flashes, osteoporosis, pathologic fractures, cognitive impairment, and depression, and it also increases risk of incident diabetes and cardiometabolic comorbidities [5]. There have also been a number of studies showing increased risk of cardiovascular morbidity and mortality with ADT use, though results of meta-analyses on this topic have been conflicting [6, 7].

A potential risk of ADT that has been investigated more recently is acute kidney injury (AKI) requiring hospitalization. Two seminal studies published within the last 8 years established this association. The first of these studies analyzed 10,250 men with newly diagnosed nonmetastatic prostate cancer from 1997 to 2008 in the UK Clinical Practice Research Datalink [8]. Using a nested case-control design, this study concluded that use of any ADT (OR 2.48, 95% CI 1.61–3.82)—in particular combined androgen blockade with gonadotropin-releasing hormone (GnRH) agonists and oral antiandrogens (OR 4.50 [95% CI, 2.61–7.78]) and GnRH agonists alone (OR 1.93 [95% CI, 1.20–3.10])—was associated with higher risk of AKI compared with no ADT [8]. Surgical castration with bilateral orchiectomy was not found to be associated with AKI. While this well-designed observational study corrected for many confounders including duration of use, comorbidities, prescription medications, procedures associated with postrenal AKI, baseline renal insufficiency, and some tumor risk factors (baseline PSA, metastasis, prostatectomy, radiation therapy, and chemotherapy during follow-up), it did not adjust for tumor stage, which is a critical confounder due to the risk of locally advanced disease causing postrenal AKI. The second study evaluated 69,292 men with newly diagnosed nonmetastatic prostate cancer from 1995 to 2009 in the SEER-Medicare database [9]. Using a propensity-matching approach, this study found that use of GnRH agonists was associated with significantly higher risk (HR 1.24, 95% CI 1.18–1.31) of AKI requiring hospitalization, with 10-year AKI rates of 30.7% in those receiving ADT vs. 24.9% in those who were ADT-naive [9]. This study was able to account for tumor grade and stage in addition to many of the major confounders mentioned above, but it did not account for duration of exposure to ADT.

There are several plausible mechanisms for why ADT may cause AKI: (A) ADT-induced hyperglycemia and dyslipidemia may affect renal glomerular function by changing the morphology of the interstitial tubular membrane, (B) ADT may blunt the vasodilation of renal vessels mediated by testosterone via nitric oxide, leading to ischemic injury, and (C) ADT-induced hypogonadism reduces estrogen, which is thought to be protective against renal ischemic injury [8].

The study by Cardwell et al. in this issue of *Prostate Cancer and Prostatic Diseases* questions the association between ADT and AKI, showing that the association did not persist in their analysis of a large registry dataset after correcting for duration of ADT exposure and tumor stage [10]. Using a case-control design analyzing 10,751 men in the Scottish Cancer Registry from 2012 to 2017, this study found that while prostate cancer patients had higher rates of AKI compared with matched cancer-free controls (HR 1.47, 95% CI 1.29–1.69), those currently using ADT (modeled as a time-varying covariate corrected for duration

✉ Timothy J. Daskivich
Timothy.Daskivich@csmc.edu

[1] Department of Surgery, Division of Urology, Cedars-Sinai Medical Center, Los Angeles, CA, USA

of exposure) did not have higher risk of AKI (HR 1.14, 95% CI 0.92–1.41). This finding held up among those receiving GnRH agonists (HR 1.13, 95% CI 0.90–1.40). It is notable that univariable models did find a higher risk of AKI with current ADT (HR 1.96, 95% CI 1.64–2.35), which persisted after correction for age, year, cancer treatment, and comorbidities, but became nonsignificant after correction for T and N stage (HR 1.14, 95% CI 0.92–1.41). The lack of association remained consistent in sensitivity analyses by type of treatment and clinically localized versus advanced disease.

While this study does not disprove the previously reported findings, it certainly opens a debate regarding the association between ADT use and AKI. Since all of the aforementioned studies are observational in nature, they are subject to selection bias, confounding by indication, inadequate assessment of duration of exposure, misclassification of ADT use or AKI outcomes, and model-related factors that may affect the observed associations. Hopefully this study will stimulate further investigation on the topic—including post hoc analysis of randomized controlled trial data—to more definitively characterize whether this association is real or merely an epiphenomenon.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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