Acute Kidney Injury with Immune Checkpoint Inhibitors
A Push beyond Case Reports

Christopher A. Carlos and Raymond K. Hsu

CJASN 14: 1679–1681, 2019. doi: https://doi.org/10.2215/CJN.12621019

Over the past decade, the development and use of targeted immunotherapies in the treatment of solid organ and hematologic malignancies have revolutionized the field of oncology. Whereas prior cancer treatments had largely relied on killing tumor cells with nonspecific cytotoxic therapies and radiotherapy, targeted immunotherapy unleashes our own adaptive immune response in preventing tumor progression. The discovery that cancers overexpress receptors designed to suppress adaptive T lymphocyte immune capabilities led to the development of so-called immune checkpoint inhibitors. Antibodies that target the cytotoxic T lymphocyte–associated protein-4, the programmed cell death 1 protein, or its ligand programmed death ligand 1 have been shown to enhance adaptive T cell activity in the tumor microenvironment.

AKI can be a dreaded and clinically important event during therapy that often prompts an interruption or even discontinuation of treatment. Perhaps thankfully, AKI was thought to be a relatively rare event associated with checkpoint inhibitors. Early estimates of AKI incidence were approximately 1%–2% in patients treated with a single agent (ipilimumab, nivolumab, or pembrolizumab) and 4.5% in those treated with the combination of nivolumab plus ipilimumab (1–3). The incidence of severe AKI (greater than or equal to threefold increase in serum creatinine or dialysis) was <1% with single agents and 1.6% with the combination of nivolumab plus ipilimumab (1–3). Regardless, as use of checkpoint inhibitors grows, recognition and understanding of its clinical pattern of nephrotoxic injury are urgently needed.

The classic mechanism of kidney injury from checkpoint inhibitors is that of acute interstitial nephritis (AIN). In 2016, Cortazar *et al*. (1) reported a patient series of 13 patients across seven centers who underwent a kidney biopsy for severe AKI during checkpoint inhibitor use. The most prevalent pathologic lesion was acute tubulointerstitial nephritis (12 of 13) characterized by diffuse interstitial infiltrates of CD3+ and CD4+ T lymphocytes (with paucity of plasma cells and eosinophils). Importantly, this patient series was the first to provide evidence of efficacy with steroids. Among the ten patients treated with steroids, nine had at least partial improvement in kidney function. AIN is now established as the primary kidney example of numerous potential immune-related adverse events (irAEs) that can affect virtually any off-target organ, including gastrointestinal tract (colitis and enteritis), liver (hepatitis), skin (dermatitis), endocrine glands (adrenalitis and thyroiditis), and lung (pneumonitis) among others, thought to represent upregulated immune system activation (4).

In this issue of *CJASN*, Seethapathy *et al*. (5) leverage comprehensive clinical data from a large tertiary oncology referral center to describe the phenotypes and predictors of AKI among just over 1000 patients treated with checkpoint inhibitors between 2011 and 2016. Among this cohort, 82 patients (8%) experienced the primary outcome of sustained AKI—defined as at least 1.5-fold rise in serum creatinine (from baseline) that persisted for ≥3 days within 1 year of treatment. Patient charts were carefully adjudicated by the investigator-nephrologists to determine whether each sustained AKI event was most likely to be "checkpoint inhibitor related" versus from another etiology (hemodynamic AKI/acute tubular necrosis, obstructive AKI, or undetermined). AKI was attributed to checkpoint inhibitor use in 30 patients (3%), occurring at a mean time of 3.5 months after commencement of therapy. The study is strengthened by its large sample size (purportedly the largest "real world" clinical cohort to date) with a wide variety of malignancies being treated; completeness and granularity in health record data, including the presentation of detailed patient summaries of checkpoint inhibitor–related AKI and descriptions of concurrent irAEs (provided in supplemental table 3 of Seethapathy *et al*. [5]); and its key capture of concomitant medications to elucidate a potentially important association. These data build on earlier biopsy patient series and pooled analyses of clinical trial data to better delineate a contemporary understanding of the epidemiology of AKI associated with immune checkpoint inhibitor treatment.

Several key findings should be highlighted (5).

The data here show that the rates of AKI during checkpoint inhibitor therapy seem to be higher than earlier reports (1–3): overall AKI incidence of 17%, sustained AKI incidence of 8%, and checkpoint inhibitor–related AKI of 3% within 1 year of treatment.

Baseline kidney function did not seem to be predictive of AKI, thus arguing that the checkpoint inhibitor therapy may be relatively safe in patients with baseline CKD

Division of Nephrology, Department of Medicine, University of California, San Francisco School of Medicine, San Francisco, California

Correspondence: Dr. Raymond K. Hsu, Division of Nephrology, Department of Medicine, University of California, San Francisco School of Medicine, 533 Parnassus Avenue, U404, San Francisco, CA 94143-0532. Email: raymond.hsu@ucsf.edu

(although it is difficult to ascertain if there is selection bias upfront; *i.e.*, clinical exclusion of patients with lower kidney function from initiation of therapy).

Checkpoint inhibitor–related AKI (*i.e.*, patients with suspected AIN cases) occurred on average ≥100 days after therapy commencement. This corroborates prior reports (1,6) also showing a delayed onset of AKI after checkpoint inhibitor initiation, suggesting a mechanism of AIN separate from or beyond direct immunogenicity of checkpoint inhibitors or their metabolites (7).

Lastly, a key finding that emerged from this study (5) is the association between baseline use of a proton pump inhibitor (PPI) and risk of AKI after prolonged exposure to checkpoint inhibitor therapy. In multivariable survival analysis taking into account competing risk of death, the investigators found that baseline PPI exposure was a strong risk factor for sustained AKI after 2.5 months of follow-up (adjusted hazard ratio, 2.85; 95% confidence interval, 1.34 to 6.08). This finding substantiates the observation from a small patient series in which five of six patients with biopsy-proven AIN from programmed cell death 1 protein inhibitor treatment had preceding exposure to PPIs (8). Again, the delayed onset of AKI after weeks to months of immune checkpoint exposure in the context of chronic PPI use points to a postulated mechanism of AIN in which checkpoint inhibitors may cause a disruption in longstanding tolerance of memory T cells primed toward PPIs. Still, better mechanistic understanding of checkpoint inhibitor–associated AIN and further validation of PPI exposure as a risk factor in other cohorts are needed before we implement widespread practice changes to strictly limit the use of PPIs before starting checkpoint inhibitors.

Significant limitations and questions remain. In this study (5), only one patient with a case of checkpoint inhibitor–related AKI was confirmed by a kidney biopsy (showing AIN). Therefore, these results assume that chart review was sufficient in accurately adjudicating patients with checkpoint inhibitor–associated AIN from other phenotypes of AKI using additional data, such as concurrent occurrence of nonkidney irAEs and response to steroids (along with pyuria, which was not always present significantly on urine microscopy). The low rate of biopsy in this study (5) may reflect lower awareness of AIN as a complication during earlier parts of the study period, but it may be fairly representative of common sense clinical practice elsewhere given inherent risks associated with kidney biopsies, especially in patients with AKI cases that are reversed readily. Recently published and slightly more contemporary biopsy patient series examining nephrotoxicities associated with checkpoint inhibitors have highlighted, interestingly, a wide range of glomerular lesions (some accompanied by interstitial inflammation) in one study (6) and high frequency of pure tubular injury (without significant interstitial nephritis) in another (9). In the absence of validated predictive biomarkers to help phenotype the type of kidney injury, it remains prudent for clinicians to pursue timely tissue diagnosis, especially in cases of severe AKI without other clear kidney insults, to help guide appropriate therapy.

Because of the time period from which the study population was derived, the study is also hindered a bit by the very small number of patients receiving programmed death ligand 1 inhibitors (4%) or a combination of checkpoint inhibitors. The usual caveats of retrospective, observational analyses using clinically obtained data apply. Because the study population does not arise from a strict integrated health care system, there is potential for ascertainment bias and underestimation of AKI incidence along with undercapture of important predictors. Despite the large overall sample size, the ultimately small number of patients with AKI (and even smaller numbers of potential checkpoint inhibitor–associated AKI) limits the investigators' ability to perform more extensive adjustments to minimize confounding. Therefore, the novel elucidation of PPIs as a risk factor for AKI in this setting may still suffer from residual confounding (and therefore, should to be validated consistently across other cohorts).

Nevertheless, this study by Seethapathy *et al.* (5) represents a significant step forward in the field of immune checkpoint inhibitor–associated nephrotoxicity and onconephrology in general. By leveraging electronic health record data from a large academic center, the investigators are able to reasonably ascertain the real world incidence of AKI using consistent definitions, describe the timing and phenotypes of AKI, and shed light on a potentially important association between PPI use and checkpoint inhibitor–associated AKI that smaller case series (include patients who developed AKI or patients who received biopsies) are unable to do. In addition to validating PPIs as a risk factor, future studies should explore additional risk factors, including how genetic determinants of autoimmune diseases may predict checkpoint inhibitor–associated AKI. Prospective studies with standardized collection of sera and urine may help to establish biomarkers to help identify AIN in this setting without tissue diagnosis (10). In terms of treatment of checkpoint inhibitor–associated AKI/AIN, we also need more data on optimal steroid dosing/length/tapering along with answers on if (and when and how) to rechallenge patients with checkpoint inhibitors after AKI, especially when potential oncologic benefits of treatment may outweigh kidney function preservation. As both oncologists and nephrologists face more AKI with ongoing growth in use of immune checkpoint inhibitors, it is now time to push beyond case reports and series.

Disclosures

Dr. Carlos has nothing to disclose. Dr. Hsu reports receiving consultancy fees from AstraZeneca and DaVita.

References

1. Cortazar FB, Marrone KA, Troxell ML, Ralto KM, Hoenig MP, Brahmer JR, Le DT, Lipson EJ, Glezerman IG, Wolchok J, Cornell LD, Feldman P, Stokes MB, Zapata SA, Hodi FS, Ott PA, Yamashita M, Leaf DE: Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. *Kidney Int* 90: 638–647, 2016
2. Wanchoo R, Karam S, Uppal NN, Barta VS, Deray G, Devoe C, Launay-Vacher V, Jhaveri KD; Cancer and Kidney International Network Workgroup on Immune Checkpoint Inhibitors: Adverse renal effects of immune checkpoint inhibitors: A narrative review. *Am J Nephrol* 45: 160–169, 2017
3. Sznol M, Ferrucci PF, Hogg D, Atkins MB, Wolter P, Guidoboni M, Lebbé C, Kirkwood JM, Schachter J, Daniels GA, Hassel J, Cebon J, Gerritsen W, Atkinson V, Thomas L, McCaffrey J, Power D, Walker D, Bhore R, Jiang J, Hodi FS, Wolchok JD: Pooled analysis safety profile of nivolumab and ipilimumab combination therapy in

patients with advanced melanoma. *J Clin Oncol* 35: 3815–3822, 2017
4. Postow MA, Sidlow R, Hellmann MD: Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med* 378: 158–168, 2018
5. Seethapathy H, Zhao S, Chute DF, Zubiri L, Oppong Y, Strohbehn I, Cortazar FB, Leaf DE, Mooradian MJ, Villani A-C, Sullivan RJ, Reynolds K, Sise ME.: The incidence, causes, and risk factors of acute kidney injury in patients receiving immune checkpoint inhibitors. *Clin J Am Soc Nephrol* 14: 1692–1700, 2019
6. Mamlouk O, Selamet U, Machado S, Abdelrahim M, Glass WF, Tchakarov A, Gaber L, Lahoti A, Workeneh B, Chen S, Lin J, Abdel-Wahab N, Tayar J, Lu H, Suarez-Almazor M, Tannir N, Yee C, Diab A, Abudayyeh A: Nephrotoxicity of immune checkpoint inhibitors beyond tubulointerstitial nephritis: Single-center experience. *J Immunother Cancer* 7: 2, 2019
7. Shingarev R, Glezerman IG: Kidney complications of immune checkpoint inhibitors: A review. *Am J Kidney Dis* 74: 529–537, 2019
8. Shirali AC, Perazella MA, Gettinger S: Association of acute interstitial nephritis with programmed cell death 1 inhibitor therapy in lung cancer patients. *Am J Kidney Dis* 68: 287–291, 2016
9. Izzedine H, Mateus C, Boutros C, Robert C, Rouvier P, Amoura Z, Mathian A: Renal effects of immune checkpoint inhibitors. *Nephrol Dial Transplant* 32: 936–942, 2017
10. Moledina DG, Wilson FP, Pober JS, Perazella MA, Singh N, Luciano RL, Obeid W, Lin H, Kuperman M, Moeckel GW, Kashgarian M, Cantley LG, Parikh CR: Urine TNF-α and IL-9 for clinical diagnosis of acute interstitial nephritis. *JCI Insight* 4: 127456, 2019

Published online ahead of print. Publication date available at www.cjasn.org.

See related article, "The Incidence, Causes, and Risk Factors of Acute Kidney Injury in Patients Receiving Immune Checkpoint Inhibitors," on pages 1692–1700.