EDITORIAL COMMENT

Checkpoint inhibitor therapy-associated acute kidney injury: time to move on to evidence-based recommendations

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment since their introduction ~15 years ago. However, these monoclonal antibodies are associated with immune-related adverse events that can also affect the kidney, resulting in acute kidney injury (AKI), which is most commonly due to acute tubulointerstitial nephritis (ATIN). Limited data are available on the true occurrence of ICI-associated AKI. Furthermore, evidence to guide the optimal management of ICI-associated AKI in clinical practice is lacking. In this issue, Oleas et al. report a single-center study of patients with nonhematologic malignancies who received ICI treatment during a 14-month period, experienced AKI and underwent a kidney biopsy at the Vall d’Hebron University Hospital. Importantly, they demonstrate that only a minority of ICI-associated AKI patients was referred to the nephrology service and kidney biopsy was only performed in 6.4% of patients. Although the authors add to our knowledge about ICI-associated AKI, their article also highlights the need for the development of noninvasive diagnostic markers for ICI-associated ATIN, the establishment of treatment protocols for ICI-associated ATIN and recommendations for optimal ICI rechallenge in patients with previous ICI-associated AKI.

Keywords: acute kidney injury, acute tubulointerstitial nephritis, immune checkpoint inhibitors, immune-related adverse events

The immune system is designed to optimally control activation and suppression of T cell function. Effective CD4 T cell activation begins with antigen recognition by the CD4 T cell in combination with major histocompatibility complex class II molecules on the cell surface of antigen-presenting cells (APCs). Additional costimulatory signaling is delivered through CD28 present on T cells, which engages CD80 or CD86 receptors on APC. Overactivation of this process is prevented by the negative feedback loop involving cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which binds to CD80 and CD86 with a much higher affinity than CD28 where an inhibitory signal is delivered to the T cell. Administering antibodies such as the immune checkpoint inhibitors (ICIs) against anti-CTLA-4 inhibits this inhibitory signal, thus resulting in prolonged T cell activation. The programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) system, which is central in the maintenance of...
T cell responses, is activated by immune responses to inflammatory cytokines. Upon engagement with PD-L1, PD-1 transmits a negative costimulatory signal to attenuate T cell activation. Antibodies directed toward PD-L1 or PD-1 will eliminate this brake, resulting in T cell reactivation. 

Many oncologists manage AKI that develops in ICI-treated patients according to the American Society of Clinical Oncology (ASCO) clinical practice guidelines, which address management of irAEs in patients treated with ICI therapy [19], and the National Comprehensive Cancer Network (NCCN) practice guidelines, which address management of immunotherapy-related adverse events (irAEs), a unique spectrum of autoimmune phenomena. The frequency and type of associated irAEs differ between the various ICIs. 

Due to their main mechanism of action, ICIs are associated with very specific side effects, termed immune-related adverse effects (irAEs), and can be either low-grade or high-grade AKI. In the study by Cortazar et al. [18], AKI was found to develop earlier in the ICI-AKI patients compared with the non-ICI-AKI patients (median 4 months [95% confidence interval (CI) 1.2–11.4] versus 8.5 months [95% CI 5.3–10.4], respectively; P = 0.026). The most frequent urine findings were subnephrotic-range proteinuria, with a mean protein:creatinine ratio of 544 mg/g and eosinophilia [5/8 patients (62%)]. In the study of Cortazar et al. [18], most patients also had subnephrotic proteinuria, approximately half had pyuria and extrarenal irAEs occurred in 43% of patients. 

The limitations of this study are worth discussing. It is a single-center study with a limited number of patients, which contrasts with recently published studies that included more patients and provided important novel data regarding the clinical/biochemical presentation, predictors of occurrence and outcome and management of ICI-associated AKI. In addition, as is problematic in other studies, a lack of kidney biopsy in patients determined to clinically have ICI-associated AKI is a limitation. This limits examination of clinical and laboratory findings as potential predictors of ATIN or another kidney lesion. However, single-center studies can be helpful to provide detailed information about the occurrence of ICI-associated AKI and current practices in the management of these patients. In addition, single-center studies can provide more detailed mechanistic insights regarding the pathophysiology of ICI-associated ATIN and identify biomarkers for a safe rechallenge with ICIs. 

Besides these mechanistic studies, international, multicenter studies are needed to establish the optimal management of ICI-associated AKI patients to optimize their cancer and kidney outcomes. 

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related toxicities [20]. The ASCO guidelines recommend a diagnostic work-up as follows: (i) exclusion of alternative etiologies of AKI (recent intravenous contrast, medications and fluid status) and (ii) monitoring of patients for elevated serum creatinine prior to every ICI dose [19]. Remarkably, routine urinalysis is not recommended other than to rule out urinary tract infections. For Grade ≥2 kidney toxicities, the guidelines recommend a nephrology consultation. In the ASCO guidelines it is explicitly stated that ‘if no potential alternative cause of AKI is identified, then one should forego biopsy and proceed directly with immunosuppressive therapy’ [19]. In the NCCN guidelines, in addition to an evaluation for alternative causes of AKI, discontinuation of nephrotoxic drugs and a spot urine protein:creatinine ratio is recommended [20]. Nephrology consultation is only recommended for Grade ≥2 kidney toxicities and kidney biopsy should be considered for Grade ≥3 kidney toxicities [20]. We believe that urinalysis (and urine sediment examination) should be performed in every ICI-treated patient with AKI. Although sterile pyuria and/or leukocyte casts lack both sensitivity and specificity for ICI-associated AKI, as noted by data showing that low-grade (tubular) proteinuria and urine abnormalities, such as pyuria and/or leukocyte casts and hematuria, occur in only approximately half and two-thirds of cases with ATIN, respectively, urinary findings can help identify non-ICI-related causes of AKI. Although both the ASCO and the NCCN guidelines recommend nephrology consultation in Grade ≥2 kidney toxicities, in actual practice this approach is rarely taken. We feel that nephrology consultation is probably not necessary in Grade 2 renal toxicities.

### Table 1. Current recommendations regarding management of AKI in ICI-treated patients

| Factor | ASCO [19] | NCCN clinical practice guidelines [20] | Perazella and Sprangers [22] |
|--------|-----------|----------------------------------------|-------------------------------|
| Severity of AKI | Consideration of potential alternative etiologies (recent intravenous contrast, medications and fluid status) and baseline renal function | Limit/discontinue nephrotoxic medication and dose adjust to creatinine clearance Evaluate potential alternative etiologies (recent intravenous contrast, medication, fluid status and urinary tract infection) Spot urine protein:creatinine ratio (proteinuria >3 g/day: check antinuclear cytoplasmic antibodies, antinuclear antibodies, double-stranded DNA, rheumatoid factor and CH50/C3/C4) | Evaluate for other causes |
| Serum creatinine 1.5–2.0 × over baseline | Consider temporarily holding ICI | Consider holding ICI Check serum creatinine and urine protein every 3–7 days | Reevaluation after 1 week and continued monitoring |
| Serum creatinine 2–3 × over baseline | Hold ICI temporarily Consult nephrology If other etiologies ruled out, administer 0.5–1 mg/kg/day prednisone equivalent If worsening or no improvement: 1–2 mg/kg/day prednisone equivalent and permanently discontinue treatment | Hold ICI treatment Consult nephrology Check serum creatinine and urine protein every 3–7 days Start prednisone 0.5–1 mg/kg/day if other causes are ruled out (treat until symptoms improve to Grade ≤1 and taper over 4–6 weeks) For persistent Grade 2 over 1 week: increase prednisone/methylprednisolone 1–2 mg/kg/day | Hold ICI treatment Consult nephrology Kidney biopsy when no other cause of AKI identified and no other irAEs present and sterile pyuria/leukocyte casts |
| Serum creatinine >3 × over baseline or >4.0 mg/dL; hospitalization indicated | Permanently discontinue ICI Consult nephrology and consider kidney biopsy Consider inpatient care Prednisone/methylprednisolone 1–2 mg/kg/day (treat until symptoms improve to Grade ≤1 and taper over 4–6 weeks) Consider other immunosuppressives if Grade >2 after 1 week of steroids (azathioprine, cyclophosphamide, cyclosporine A, infliximab and mycophenolate mofetil) | Permanently discontinue ICI Consult nephrology and consider kidney biopsy Consider inpatient care Prednisone/methylprednisolone 1–2 mg/kg/day (treat until symptoms improve to Grade ≤1 and taper over 4–6 weeks) Consider other immunosuppressives if Grade >2 after 1 week of steroids (azathioprine, cyclophosphamide, cyclosporine A, infliximab and mycophenolate mofetil) | Halt ICI treatment Consult nephrology Kidney biopsy when no other cause of AKI identified and no other irAEs present and sterile pyuria/leukocyte casts |
| Life-threatening consequences, dialysis indicated | Consult nephrology Administer corticosteroids (initial dose of 1–2 mg/kg/day prednisone or equivalent) | | |
toxicities when an alternative cause of AKI is clearly identified (renal obstruction, hypotension with ischemic acute tubular injury, etc.). In our opinion, kidney biopsy should be performed in ICI-treated patients with Grade ≥2 kidney toxicity when no potential alternative causes of AKI are identified and before treatment with corticosteroids is initiated. The histological information will help guide therapy, as finding non-ATIN lesions reduces unnecessary and potentially harmful corticosteroid exposure in cancer patients and may permit continued ICI use.

In ICI-treated patients with AKI where immunosuppressive treatment needs to be initiated to treat extrarenal irAEs, we recommend postponing kidney biopsy and observing the evolution of kidney function. Kidney biopsy would be recommended when there is no kidney function recovery with immunosuppressive treatment. Recently urinary interleukin-9 and tumor necrosis factor α have been suggested as markers to effectively differentiate between ATIN, acute tubular injury and other kidney lesions [21]. Further research is needed to validate these markers as diagnostic markers of ICI-associated ATIN and to provide clinicians with a useful noninvasive diagnostic tool.

In regards to therapy, the ASCO and NCCN guidelines recommend temporary cessation of ICI treatment and, when no other etiologies can be identified, the administration of 0.5–1 mg/kg/day prednisone equivalents for Grade 2 kidney toxicities (Table 1). With no improvement in kidney function, it is recommended that the dose of corticosteroid be increased to 1–2 mg/kg prednisone or equivalent in combination with ICI discontinuation. When there is a kidney recovery to Grade 1 or less, corticosteroids should be tapered over 4–6 weeks. For Grades 3–4 kidney toxicities, permanent discontinuation of ICI treatment is recommended in combination with a nephrology consultation, evaluation for other etiologies and initiation of 1–2 mg/kg/day prednisone or equivalent when no other identifiable etiologies exist. All of these interventions presume that all Grade ≥2 kidney toxicities without an alternative cause are ATIN. Given the nonspecific signs and symptoms of kidney injury, as well as multiple competing causes of AKI in cancer patients, we believe kidney biopsy is of far greater importance than suggested by these guidelines, not only to make a correct diagnosis, but—more importantly—to guide treatment regarding ICI discontinuation, treatment with corticosteroids and ICI rechallenge. Although corticosteroid treatment may not affect oncologic outcomes, they are still associated with an increased incidence of sepsis, venous thromboembolism and fractures in population-based cohort studies, even in patients with short and moderate corticosteroid exposure [23]. In the study by Oleas et al. [16], three patients (37%) received treatment with pulses of methylprednisolone 250–500 mg/day and five patients (62%) received prednisone 1 mg/kg/day. Seven of eight patients (87%) experienced recovery of kidney function and one patient (12%) progressed to chronic kidney disease. In the study by Cortazar et al. [18], most patients (86%) were treated with steroids and complete or partial recovery was obtained in 40 and 45%, respectively. Predictors of improved kidney prognosis included

Table 2. Current recommendations regarding rechallenge with ICI in patients with previous AKI

| Factor | ASCO [19] | NCCN clinical practice guidelines [20] | Perazella and Sprangers [22] |
|--------|-----------|--------------------------------------|-------------------------------|
| Serum creatinine 1.5–2.0 × over baseline | If improved to baseline, resume routine creatinine monitoring | Upon resolution to Grade ≤1, consider resuming concomitant with steroid if creatinine is stable | Resolves: continue ICI treatment |
| Serum creatinine 2–3 × over baseline | If improved to Grade 1, taper corticosteroids over at least 3 weeks before resuming treatment with routine creatinine monitoring | Upon resolution to Grade ≤1, consider resuming concomitant with steroid if creatinine is stable | Progresses: stop ICI treatment |
| Serum creatinine ≥3 × over baseline or >4.0 mg/dL; hospitalization indicated | If improved to Grade 1, taper corticosteroids over at least 4 weeks If elevations persist >3–5 days or worse, consider additional immunosuppression (e.g. mycophenolate) | Permanent discontinuation of ICI is warranted in the setting of severe (Grades 3–4) proteinuria | Non-ICI-related: restart ICI when AKI resolves |
| Life-threatening consequences, dialysis indicated | If improved to Grade 1, taper corticosteroids over at least 4 weeks If elevations persist >2–3 days or worse, consider additional immunosuppression (e.g. mycophenolate) | Permanent discontinuation of ICI is warranted in the setting of severe (Grades 3–4) proteinuria | ICI-related and biopsy: no ATIN: restart ICI when AKI resolves; ATIN: treat with steroids and restart ICI when AKI resolves |
concomitant TIN-causing medications prior to AKI and treatment with corticosteroids. Failure to achieve kidney recovery after ICI-associated AKI was independently associated with higher mortality [18].

Another important issue is whether ICI treatment can be safely reinitiated after ICI-associated AKI. The ASCO and NCCN guidelines recommend permanent discontinuation of ICI treatment in patients with Grades 3–4 kidney toxicities (Table 2). For patients with Grade 2 kidney toxicities, ICI rechallenge can be considered after discussion with the patient when there is neither recurrence nor CKD [19]. Recently Allouchery et al. [24] reported an analysis based on the French pharmacovigilance database evaluating ICI-treated patients with at least one Grade ≥2 irAE resulting in ICI discontinuation, with subsequent ICI rechallenge. The authors demonstrated that 61.1% of the patients who discontinued ICI treatment for Grade ≥2 irAEs experienced no recurrent Grade ≥2 irAEs after ICI rechallenge [24]. In the study of Cortazar et al. [18], ICI rechallenge was performed in 22% of patients, of whom only 23% developed recurrent AKI. In the study by Isik et al. [17], rechallenge with an ICI was attempted in 16 (43%) of the ICI-AKI patients and recurrence was reported in 3 (19%) of the rechallenged patients. Interestingly, in this study, survival tended to be higher in the group not rechallenged compared with the group that was rechallenged; however, results were not statistically significant [17]. So the risk of recurrence appeared to be acceptable and, as such, we do not agree with the ASCO and NCCN guidelines. In contrast, we recommend ICI reinitiation in all patients where an alternative cause of AKI has been identified [22]. Also, in patients with histology-proven ICI-associated ATIN, we recommend rechallenge with ICI with close monitoring after kidney function recovery. Although not supported by data, clinicians may consider using low-dose corticosteroids in patients with ATIN who had Grade ≥3 kidney toxicities.

In conclusion, the study of Oleas et al. [16] further adds to the existing evidence regarding the frequency, diagnosis and management of ICI-associated AKI in clinical practice. In this area, single-center studies can be helpful to provide more detailed mechanistic insights regarding the pathophysiology of ICI-associated ATIN and identify biomarkers for safe rechallenge with ICI. Additionally, international, multicenter studies are needed to establish the optimal management of ICI-associated AKI patients to optimize their cancer and renal outcomes. Importantly, an evidence-based approach is required to facilitate the creation of rigorous guidelines on the appropriate clinical approach for ICI-associated kidney toxicity.

**CONFLICT OF INTEREST STATEMENT**

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