

Kidney Biopsy Should Be Performed to Document the Cause of Immune Checkpoint Inhibitor–Associated Acute Kidney Injury: PRO

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Introduction

Immune checkpoint inhibitors (CPIs) have significantly improved the outcome for patients with cancer by effectively overcoming cancer resistance by allowing the host immune system to recognize and eliminate tumor cells. Immune checkpoints are regulatory receptors and ligands that allow immune-mediated destruction of foreign antigens while at the same time prevent autoimmune host organ injury. CPIs remove these breaks on the immune system and, not unexpectedly, are associated with the development of immune-related adverse events (IRAEs). IRAEs are common with grade 3/4 toxicities developing in approximately 20% of patients. Skin, gastrointestinal tract, and endocrine IRAEs are most frequent; whereas IRAEs affecting the kidney are less common: 1%–2% with monotherapy and 5% with combined immune CPIs (1), although this is likely an underestimate (2). Various types of kidney injury have been described including acute tubulointerstitial nephritis (ATIN), acute tubular injury, glomerular diseases, and thrombotic microangiopathy (3). The 2017 American Society of Clinical Oncology (ASCO) guideline on the treatment of IRAEs describes the expert consensus on the approach of organ-specific events (4). The guidelines recommend that if causes of AKI other than IRAEs have been eliminated, the physician should forego the need for biopsy and proceed with immunosuppressive therapy. According to this guideline, no other urinalysis is indicated but the nephrologist may consider further investigation. As far as kidney IRAEs are concerned, clinical findings and laboratory tests are suboptimal in predicting the precise underlying kidney lesion, making kidney biopsy necessary in the majority of cases to definitely diagnose the precise lesion, to guide therapy, and—possibly—to improve the overall outcome in patients treated with CPIs.

Cases

Case 1: A patient with nonsmall cell lung cancer was referred to the nephrology outpatient clinic with an increase in serum creatinine (1.1–2.0 mg/dl) over a

period of 3 months. Onset of renal-function loss occurred approximately 5 months after start of nivolumab (anti-programmed cell death protein 1) at a dose of 3 mg/kg (174 mg) every 2 weeks. Clinical presentation included *de novo* hypertension and malaise. Retrospectively, urinalysis over the last months showed a conversion from negative for albumin to 2+. Incomplete 24-hour urine collection showed 1.5 g of proteinuria per day. Earlier low-grade IRAEs included skin toxicity and hyperthyroidism.

Case 2: A patient with metastatic Merkel cell carcinoma was admitted for a rise in creatinine (1.0–1.8 mg/dl) over a period of 4 weeks and malaise with nausea and limited intake. Avelumab (anti-programmed death-ligand 1) 10 mg/kg (910 mg) every 2 weeks was started 4 months before onset of renal-function loss. Postrenal obstruction was excluded. Abdominal ultrasound showed a collapsing vena cava. There was no documented hypotension or tachycardia. Rehydration with intravenous saline did not result in improvement of renal function with progressive rise in serum creatinine (2.2 mg/dl) over the next days. Dipstick urinalysis showed 1+ proteinuria and no erythrocyturia or leukocyturia. There were no signs of other IRAEs.

ATIN Is the Most Common IRAE but Also Other Kidney Adverse Events Occur in Patients on CPI Therapy

Various types of kidney adverse events (AEs) have been reported in patients treated with CPI. ATIN is the most common form of kidney disease, with glomerular lesions (isolated or with acute tubular injury), isolated acute tubular injury, and nonspecific lesions also being observed (Table 1). Kidney injury is common in patients with cancer and often multifactorial (5). In patients with cancer who are treated with CPIs, kidney injury unrelated to CPIs can occur including nephrotoxic kidney injury, ischemic tubular injury, paraneoplastic kidney damage, crystalline nephropathy, and postrenal AKI. A recent retrospective observational study showed that, in the first year after initiation of CPIs, 8% encountered a sustained AKI episode. After

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careful record evaluation, 3% (one in three to four sustained AKI episodes) was judged as an IRAE; however, no structural pathology data was available to validate this (6). Therefore, patients with cancer and kidney injury should undergo a careful evaluation for potential causes to make the correct diagnosis to guide appropriate management.

Not Performing a Biopsy Will Result in an Erroneous Diagnosis in a Significant Subset of Patients

Clinical findings and laboratory tests are suboptimal in predicting the underlying kidney lesion in patients treated with CPIs who are experiencing kidney injury. The occurrence of other organ IRAEs are not helpful in predicting the presence of ATIN because less than half of patients with a documented kidney lesion had another extrarenal manifestation. Low-grade 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. For these reasons, it cannot be assumed that all kidney injury occurring in patients receiving CPIs is due to ATIN, and a kidney biopsy is necessary in the majority of patients to establish a correct diagnosis. Recently, urinary IL-9 and TNF- α have been reported to effectively distinguish ATIN from acute tubular injury and other renal lesions (7). Further studies are needed to evaluate whether these represent a noninvasive test to identify ATIN in patients treated with CPIs and allow for differentiation between ATIN and other kidney lesions in patients with cancer who are treated with CPIs.

Current Guidelines Do Not Value Kidney Biopsy Sufficiently

Our recommendation is not in line with current recommendations and, likely, current clinical practice. The ASCO

guidelines on the management of IRAEs in patients treated with immune CPI therapy (CPIT) suggest a nephrology consult for greater than stage 2 AKI and recommend against a kidney biopsy if other causes of AKI can be excluded on clinical grounds (4). Moreover, it recommends withholding CPIT for patients developing grade 2 Common Terminology Criteria for AEs (CTCAE) complications until at least partial improvement (4). Oral corticosteroids are given for patients whose symptoms persist for >1 week. For those developing grade 3 and 4 complications, CPIT is discontinued and a more intensive corticosteroid regimen is administered. All of these therapeutic measures presume that all CTCAE kidney complications are caused by ATIN. Given the nonspecific signs and symptoms of kidney injury, as well as multiple competing causes of kidney injury in patients with metastatic cancer, we believe a kidney biopsy is of far greater importance than suggested by the guidelines, not only to make a correct diagnosis but—more importantly—to guide treatment regarding discontinuation of CPIs, administration of corticosteroids, and reinitiating CPIs.

Histologic Diagnosis Is Necessary to Guide Treatment (or not)

If ATIN or another immune-mediated lesion is observed on the biopsy sample in a patient with AKI, the immune CPI should be held, any other drugs associated with ATIN discontinued, and corticosteroids administered. In the literature, CPIT was discontinued in the majority of cases (approximately 90%) in patients treated with CPIs experiencing AKI, while corticosteroids (oral and/or intravenous) were also administered in approximately 80% of patients. Interruption of CPI and/or administration of corticosteroids in patients with non-IRAE can result in both inferior cancer outcomes and side effects. CPIs are among the most effective available cancer treatments. Unnecessarily withholding them because of presumed IRAEs will compromise patient outcomes. Corticosteroid treatment by itself appears to be harmless as far as oncologic outcomes are concerned. In population-based cohort studies published on the short-term use of oral corticosteroid-related harms, there was an increased incidence of sepsis, venous thromboembolism, and fractures (8). Patients in this study had been on steroid therapy for an average of 6 days as compared with the duration for patients with renal IRAEs, which is usually for 4–6 weeks. The maximum dosage in the cohort study was 40 mg/day as compared with the dosages for IRAEs, which is 1–2 mg/kg per day. This risk increases in those with diabetes, as studied by the same authors (9).

CPI Retreatment in Patients with Previous Kidney IRAEs

Whether CPIs can be reinitiated in patients experiencing AKI during CPI treatment remains a matter of intense debate. In patients where ATIN or another immune-mediated lesion is not seen on biopsy, the CPI can be reinitiated and corticosteroids can be avoided unless there are other IRAEs present. A precise diagnosis based on kidney biopsy thus reduces unnecessary and potentially harmful corticosteroid exposure and allows for continued

Table 1. Characteristics of histologic findings in published case series

Reference	CPI	Other ATIN Drugs	Kidney Biopsy
Shirali <i>et al.</i> (10) (n=6)	3 Nivo 2 Pembro 1 Ipi+nivo	5 PPI 1 NSAID	6 ATIN
Cortazar <i>et al.</i> (1) (n=13)	6 Ipi 1 Nivo 2 Pembro 4 Ipi+nivo	6 PPI 1 NSAID 3 Antibiotics	12 ATIN 1 TMA
Izzedine <i>et al.</i> (18) (n=12)	12 Pembro	0	5 ATI 4 ATIN 1 MCD+ATI 1 MCD 1 NF
Mamlouk <i>et al.</i> (17) (n=16)	6 Nivo 6 Pembro 2 Ipi+nivo 1 Atez 1 Trem	9 PPI 3 NSAID 3 Antibiotics	5 ATIN 9 ATIN+GN 1 ATI 1 NF

CPI, checkpoint inhibitor; nivo, nivolumab; PPI, proton pump inhibitor; ATIN, acute tubulointerstitial nephritis; pembro, pembrolizumab; NSAID, nonsteroidal anti-inflammatory drug; ipi, ipilimumab; TMA, thrombotic microangiopathy; ATI, acute tubular injury; MCD, minimal change disease; NF, nonspecific findings; atez, atezolizumab; trem, tremelimumab.

use of CPIs. It has been recommended that, in patients who demonstrate objective response to immunotherapy and develop IRAEs of up to grade 3 severity, immunotherapy can generally be restarted if IRAE severity reverts to grade 1 or less, especially in patients with limited treatment options (4). Oncologists are more aggressive in their treatment approach than nephrologists and are eager to restart either the same immunotherapy drug or switch to a different one, sometimes concurrently with low-dose prednisone after AKI reverts to CTCAE grade 1 or lower. However, in published reports, there are only three patients with biopsy-confirmed ATIN reported to have continued or resumed immunotherapy after recovering from AKI without subsequent deterioration in kidney function (1,10).

Interestingly, in patients receiving CPIs, objective response rate, overall survival, and time to treatment failure do not seem to be negatively affected by the development of IRAEs (11,12). Moreover, there is limited data suggesting that outcomes are improved in patients experiencing IRAEs, irrespective of whether CPIs are reinitiated (13–16). Whether this also holds true for patients experiencing kidney IRAEs needs to be established. To be able to study this, a precise diagnosis (and exclusion of non-IRAEs) requiring a kidney biopsy is necessary. If proven valid it might not be necessary to try to reinitiate CPIs in patients with previous IRAEs.

Discussion of Cases

In the case of our first presented patient, there were clinical signs for a nephrologist to suspect a glomerular disease. This patient presented with rapidly progressive kidney function loss, but not as acute as expected for a traditional ATIN—the hallmark form of IRAE kidney injury during CPI use. However, slower progressive forms of ATIN have been observed. The kidney biopsy sample showed widespread FSGS (not otherwise specified) with a mild tubulointerstitial nephritis. Treatment with high-dose steroids over a prolonged period only resulted in stabilization of renal function after a further increase in serum creatinine after initiation of antihypertensive and antiproteinuric therapy. The patient died due to complications of a liver metastasis which resulted in obstructive jaundice.

So, this patient had a predominant glomerular disease as renal IRAE. One should not ignore that, in the case series of Cortazar *et al.* (1), one out of the 13 subjects reported had a glomerular disease, namely a thrombotic microangiopathy. Case reports have described a variety of glomerular pathology during CPI treatment. Mamlouk *et al.* (17) reviewed a series of biopsy samples and observed a high frequency of glomerular pathology in different grades of severity next to dominant or only mild ATIN, in line with the results of the presented case. The unstructured approach to performing biopsies in the setting of kidney injury during CPIT could influence findings in these case series due to confounding by indication. To get a more profound understanding of the frequency of relevant glomerular pathology, we need a more structured approach for setting an indication for renal biopsies. In addition, the presence of glomerular pathology can be of relevance in understanding (non-)response to steroid treatment or second-line therapy choices

The second patient's kidney biopsy showed a predominant acute tubular injury pattern with limited interstitial inflammation. There was no documented period of hypotension or other prominent cause for this finding. He used a proton pump inhibitor given the gastric location of a large metastasis which could be a risk factor for AKI during CPIT (6). Despite these findings, high-dose steroids (1 mg/kg) were prescribed. After 1 month he was admitted to the intensive care unit with a steroid-induced cardiac asthma.

In 2019, several reports of acute tubular injury as the main finding in renal biopsies were published. First described by Izzedine *et al.* (18), but also reported by Mamlouk *et al.* (17) and Cassol *et al.* (19) in their case series, acute tubular injury was observed with only modest inflammation in a substantial proportion of cases. It is not clear that this is an immune-mediated entity, as supported by the immunohistochemical findings (19). More experience is needed in the natural course of tubular injury with limited interstitial inflammation during CPIT use.

Conclusions

Clinical findings and laboratory tests do not allow us to make a precise diagnosis in patients receiving CPI experiencing kidney injury. Therefore, a kidney biopsy is necessary in the majority of cases to definitely diagnose the precise lesion, to guide therapy, and—possibly—to improve the overall outcome in patients treated with CPIs. A kidney biopsy can only be waived in patients with clear postrenal or prerenal causes of AKI (in whom CPIT should be continued and no corticosteroids administered), in patients who refuse to undergo kidney biopsies, or in cases where it is unsafe to perform a kidney biopsy. A possible approach to patients treated with CPIs experiencing AKI has been published and discussed previously (3). If the cancer patient is responding well to immunotherapy and there are no other viable options for the patient, the following approach to therapy is reasonable. Patients with stage 1 AKI or isolated proteinuria can be continued on immune CPIT and observed while searching for reversible causes of AKI. If the patient has a progression to a higher stage AKI or presents with stage 2 or 3 AKI, the immune CPI should be discontinued. In this setting, knowledge of the underlying kidney lesion (ATIN versus acute tubular injury versus glomerulopathy versus something else) is clearly preferable and a kidney biopsy is highly recommended. Empirical therapy for AKI and/or proteinuric lesions with corticosteroids without securing a definitive diagnosis is suboptimal and potentially harmful. This approach may expose patients without an immune-mediated lesion to corticosteroids (with the associated complications) unnecessarily. In patients with nonimmune-mediated AKI during CPIT, CPIT should be continued to maintain anticancer responses.

Author Contributions

M. Eijgelsheim and B. Sprangers conceptualized the study, wrote the original draft of the manuscript, and reviewed and edited the manuscript.

Disclosures

B. Sprangers is a senior clinical investigator of The Research Foundation Flanders (Fonds voor Wetenschappelijk Onderzoek – Vlaanderen; FWO) (1842919N). M. Eijgelsheim has nothing to disclose.

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See related commentary, “Kidney Biopsy Should Be Performed to Document the Cause of Immune Checkpoint Inhibitor–Associated Acute Kidney Injury: Commentary” and debate, “Kidney Biopsy Should Be Performed to Document the Cause of Immune Checkpoint Inhibitor–Associated Acute Kidney Injury: CON,” on pages 166–168 and 162–165, respectively.