Acute Renal Failure After Treatment with a Combination of Immune Checkpoint Inhibitors in a Patient with Renal Cell Cancer

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Abstract

In the United States, Diabetic Kidney Disease (DKD) is one of the most common causes of Chronic Kidney Disease (CKD). DKD is assumed to be caused mostly by chronic hyperglycemic conditions. Clinically, however, achieving glycemic control in people with diabetes is difficult. Recent breakthroughs in mitochondrial biology have given us a new perspective on mitochondrial malfunction in DKD. A range of diabetes problems, including DKD, have been linked to reduced mitochondrial activity; moreover, aberrant mitochondrial fission may play a role in DKD development. Metformin or Sodium-Glucose coTransporter 2 (SGLT2) inhibitors have been shown to protect the kidneys by enhancing mitochondrial dynamics and lowering oxidative stress. As a result, medicines that target mitochondrial function restoration may become innovative treatment agents for DKD. Imeglimin is the first of a new family of oral anti-diabetic medications that can lower reactive oxygen species and boost mitochondrial DNA synthesis. The possible treatment strategies that impact mitochondrial activity and prevent DKD are discussed in this review.

Keywords: Diabetic Kidney Disease (DKD) • Imeglimin • Metformin • Mitochondrial function • Reactive oxygen species (ROS) • Sodium-glucose co-transporter 2 (SGLT2)

Perspective

Recent breakthroughs in immunotherapy have showed considerable promise, particularly in the case of renal cell carcinoma, which is renowned for having a highly immunogenic tumor microenvironment. Recent trial outcomes suggest that combined immune checkpoint inhibition with nivolumab and ipilimumab will soon be utilized as a first-line therapy for advanced renal cell carcinoma. However, because dual immune checkpoint blockade may exacerbate the effects and lead to more severe immune-related side events, we recommend vigilant monitoring and vigilance with such medicines. We describe a case of a patient who had acute renal failure and required dialysis after starting combination immune checkpoint inhibitor medication. Our experience demonstrates the need for a more proactive approach to immune-related adverse events prevention and monitoring. Given their greater sensitivity to renal insult in the setting of recent surgical procedures and underlying malignancy, we sought to emphasize the concern for nephrotoxic events in renal cell carcinoma patients.

Renal Cell Carcinoma (RCC) is a fast expanding cancer diagnosis in the industrialized world, and it is now the ninth most common cancer diagnosis and the most prevalent urological malignancy in the United States. This is especially concerning because late-stage RCC has a dismal 5-year survival rate of about 12%, however because to breakthroughs in systemic therapy, the death rate has happily plateaued. One of these breakthroughs is the addition of Immune Checkpoint Inhibitors (ICI) to our therapy arsenal. RCC is a prime target for immunotherapy since it is widely recognized to be a highly immunogenic tumor, and cytokine-based therapies such as high-dose IL2 were one of the first treatments employed. They do, however, have clinically significant side effects that may have long-term ramifications. Despite this, ICI treatment has no official contraindications, even in those who are at high risk of developing an immune-related adverse event, because the potential therapeutic benefits significantly exceed the dangers.

A 65-year-old man with a history of HIV (compliant on HAART therapy with undetectable viral load), hypertension, hyperlipidemia, type 2 diabetes, chronic obstructive pulmonary disease, peripheral arterial disease, and clear cell renal carcinoma (pT3N1M1) status following left nephrectomy presented to the emergency room with weakness for two weeks, as well as bilateral lower extremity edoema and dyspnea on exertion. With the exception of a 90% oxygen saturation, the patient's vital signs were within normal norms. The potassium level was 8 mmol/l, the creatinine level was 10 mg/dl, and the bicarbonate level was 9 mmol/l, all suggesting severe acute renal damage, according to the patient's metabolic panel. A fresh 1st degree AV block and enlarged QRS complexes were discovered on an ECG. For cardiac membrane stability, the patient was administered insulin/dextrose 50 percent in water, albuterol, furosemide, and sodium zirconium cyclosilicate with calcium gluconate. The patient was transported to the intensive care unit for emergency hemodialysis when the repeat potassium level remained elevated at 7 mmol/l. The patient's potassium level stabilized at 5.4 mmol/l after dialysis, however his creatinine level remained excessive, fluctuating from 5 mg/dl to 8 mg/dl. Regarding the patient's cancer history, he had just recently been diagnosed five months prior to presentation when he came for stomach discomfort and bloating at an outside hospital. A massive left renal tumor, compatible with renal cell carcinoma, was seen on imaging. He was then sent to our facility for a more thorough examination and treatment plan. Following that, the patient was started on a regimen of nivolumab 3 mg/kg IV + ipilimumab 1 mg/kg q3week cycles, which began one month previous to admission.

The aetiology of the AKI was determined after a thorough investigation. Only modest leukocytes and negative nitrites were found in the urine. There was no proteinuria, ruling out nephrotic syndrome. There were 31–50 WBC per high power field in urine microscopy, but no granular casts were seen. The fractional excretion of sodium was computed and found to be 1.8 percent, which is consistent with intrinsic renal disease. An ultrasonography of the right kidney revealed a normal size and no acute abnormalities. Since he began following within our system roughly 3 months before to presentation, the patient had a baseline increased creatinine level of around 2 mg/dl. His creatinine level remained steady until the day of his admittance, when it suddenly increased. The patient's anti-retroviral medication, which includes tenofovir, was explored as one probable cause for his acute renal failure. Tenofovir's nephrotoxicity, on the other hand, is usually caused by the drug's tendency to damage the proximal renal tubules, which might result in acquired Fanconi syndrome. More urine electrolyte assays were acquired to further analyze this, but they did not reveal glycosuria, phosphaturia, or hyperuricosuria, which would have been consistent with a Fanconi syndrome. Furthermore, the patient has been taking this drug for a long time with no problems. His recent left nephrectomy, which had been done two months before to presentation, was also considered as a probable explanation.

Given the chronology and severity of the renal failure, this scenario appeared improbable. In addition, a renal artery ultrasonography revealed no abnormalities, including the absence of any suspected post-operative stenosis. His recent commencement of combination ICI treatment was another option. Only two weeks before his hospitalization, he received cycle. Our concerns were confirmed by an earlier urine study that revealed sterile pyuria and additional urine tests that revealed eosinophiluria, both of which were compatible with a diagnosis of acute interstitial nephritis (AIN), a pattern of damage that can be observed with PDL-1/CTLA-4 inhibitors. Although a kidney biopsy was planned for confirmation of the diagnosis, it was postponed due to the patient's history of nephrectomy and now single kidney. Unfortunately, after consulting oncology and

nephrology, it was discovered that the patient's kidney function had been irreversibly damaged. As a result, steroids were postponed, and a permanent catheter was implanted to allow for outpatient dialysis. His renal function would be constantly monitored, and he would be referred to oncology for future treatment choices.

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