

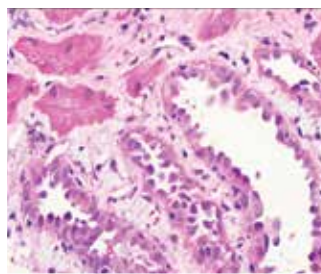
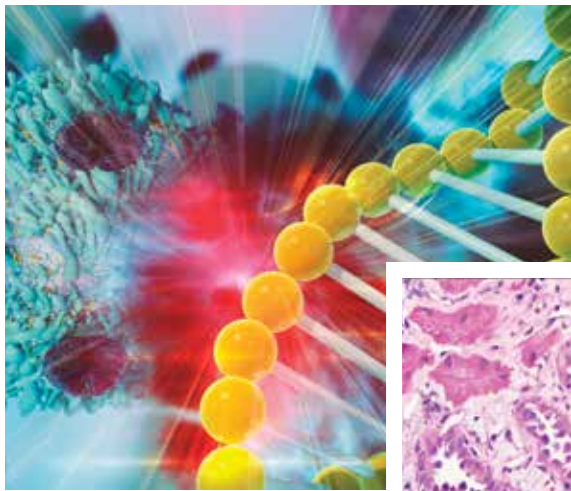


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Immune Checkpoint Inhibitors for Cancer Treatment Have Renal Side Effects

By Eric Seaborg



Courtesy Ala Abudayyeh

Immunotherapy has successfully treated several recalcitrant forms of cancers and is on the cusp of revolutionizing treatment. But as with any new therapy, greater use is revealing side effects that must be managed, including dangers to the kidney.

Nephrologists need to be aware of these potential prob-

lems and the ways to counter them, according to Kenar D. Jhaveri, MD, professor of medicine in the division of kidney diseases and hypertension at Hofstra Northwell School of Medicine in Great Neck, N.Y. The most common of these problems are immune-mediated, including acute interstitial nephritis (AIN) and glomerular diseases, both of which can generally be countered with corticosteroids.

Immunotherapy is effective because it attacks cancer's secret weapon—its ability to hide from the immune system by keeping immune cells from recognizing cancer cells as invaders. The immune system is full of checks and balances to keep the body from attacking itself, and several years ago researchers discovered some of the “checkpoints” on T cells that act as brakes on their aggressiveness, including the proteins PD-1 (for programmed cell death 1), PD-L1, and CTLA-4 (for cytotoxic T-lymphocyte-associated protein 4). Many tumor cells express the ligands for these checkpoint receptors, and when triggered, the checkpoint proteins provide a brake or “off switch” that inhibits the T cell from attacking the tumor cell (Figure 1).

Researchers next developed drugs they dubbed immune checkpoint (ICP) inhibitors—monoclonal antibodies aimed at PD-1, PD-L1, and CTLA-4 that block them from binding to the tumor cells, thereby taking off the brake and allowing the T cell to recognize and attack tumor cells (Table 1).

“The U.S. Food and Drug Administration has approved ICP inhibitors for advanced or metastatic melanoma, non-small cell lung cancer, recurrent head and neck cancer, kidney cancer, urothelial cancer, and Hodgkin lymphoma,” said Umut Selamet, MD, clinical instructor of nephrology and director of the onco-nephrology program at the University of California at Los Angeles. Selamet conducted most of her work on immune checkpoint inhibitors during her training at MD Anderson Cancer Center, with Ala Abudayyeh, MD, associate professor of nephrology at the University of Texas MD Anderson Cancer Center.

As one might expect, when more patients receive the drugs, their side effects come into better focus. And as these drugs take the brakes off the T cells, the cells may attack the patient's own tissues—and the kidneys are of particular concern.

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Proactive Nephrology Teams Leverage Electronic Tools to Prevent AKI

By Bridget M. Kuehn

By 6 a.m. each morning, an electronic dashboard displaying real-time information about the 8 to 10 patients at highest risk for acute kidney injury (AKI) is available for review by the nephrologists at Phoenix Children's Hospital.

“We have an entire day's work cut out for us and see who needs the attention,” said Kanwel Kher, MD, chief of the division of nephrology at the hospital. “We have to evaluate them quickly, we can do that in about 10 to 15 minutes.”

The nephrologists can access patients' complete charts

through links in the dashboard, which is integrated with the hospital's electronic medical record system (EMR). Using a secure text message system, Kher and his colleagues can send their recommendations for reducing the patient's risk of AKI directly to the child's attending physician.

The effort is part of a growing movement in the field of nephrology to use electronic records, e-alerts, and other tools to more proactively prevent AKI and its progression in hospitalized patients. So far, the data on using e-alerts have been mixed. But some initiatives leveraging electronic

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ICP inhibitors and transplant patients

Considering that immunosuppression is a key to transplant success, it is not surprising that ramping up the immune system with ICP inhibitors can cause problems for transplant patients. CTLA-4 inhibitors have been successfully used in kidney, liver, and heart transplant patients without rejection,” according to a review that Jhaveri and colleagues published in the *Journal of Onco-Nephrology*.

“PD-1 inhibitors and the combination therapy of CTLA-4 and PD-1 inhibitors have been associated with cellular- and antibody-mediated rejection,” Jhaveri said.

Jhaveri has also published a case of a kidney transplant patient who developed cancer, for which he was treated with a PD-1 inhibitor. The care team gave the patient a pre-emptive regimen of glucocorticoid and sirolimus, and he experienced no adverse immune response around the kidney transplant.

Table 1. FDA-approved ICP inhibitors

Anti-CTLA-4 drugs: Ipilimumab

Anti PD-1 drugs: Nivolumab, Pembrolizumab

Anti PD-L1 drugs: Atezolizumab, Durvalumab, Avelumab

Abbreviation: ICP = immune checkpoint

Immune-mediated effects

“The ICP-inhibitor–related problems are similar to those of other immune-mediated kidney conditions, as well as acute kidney reactions associated with antibiotics and proton pump inhibitors,” Selamet said.

The main adverse effect associated with both the PD-1 inhibitors is AIN, and the main toxicities associated with the CTLA-4 inhibitor ipilimumab are AIN, glomerular diseases, and hyponatremia, according to Jhaveri. PD-1 inhibitors have been associated with acute graft loss in organ transplant patients, although solo use of CTLA-4 inhibitors has not.

The kidney injury develops more slowly for PD-1 inhibitors, at three to 10 months from the start of treatment, compared with CTLA-4 inhibitors, at two to three months.

The earliest and most obvious sign of a problem is a rise in serum creatinine, although “in urinalysis you may start to see some protein spilling, proteinuria, and sometimes hematuria and white blood cells in the urine,” Selamet said. These signs should lead to the gold standard for diagnosis—a kidney biopsy.

Treatment for ICP-inhibitor–caused AIN and glomerular nephritis is similar to that of other immune-mediated AIN, consisting of a course of corticosteroids. “Some patients benefit from a short course of six weeks. Some patients need a full course of three months. And some are even extended to six months,” Selamet said. She notes that the glomerular nephritis is generally harder to treat than AIN, and may require longer treatment, but that most cases lead to complete kidney recovery.

The rarer side effect of hyponatremia could be symptomatic of an endocrine problem. Hyponatremia can occur in cancer patients due to a syndrome of inappropriate antidiuretic hormone release, which may require intervention by an endocrinologist, Selamet said.

The first studies found the incidence of the side effects to be around 1 to 3%, but more recent studies suggest that it could be as high as 10 to 30%, Jhaveri said. It’s hard to get a good handle on the rate of true injury, because some reports may rely on elevated lab tests without confirming the extent or source of the problem.

“A lot of times, the oncologists don’t even call the nephrologists,” Jhaveri said. “They see an increase in creatinine, and they just start treating with steroids, because they as-

sume they know what it is. But it is not always the case. You can have other causes of kidney injury in a patient getting these drugs. Kidney biopsies are the definitive way to diagnose them.”

Effects beyond the kidney

Kidney problems may be among the easier to spot because patients on immunotherapy receive regular lab workups that include renal tests. Cardiac problems are also common, and some of the most vulnerable other tissues are in the endocrine system, including the thyroid, pituitary, pancreas, and adrenal gland.

Patients have more generalized reactions as well. “We are seeing a number of nonspecific symptoms with these drugs, things like fatigue,” said Howard Kaufman, MD, immediate past president of the Society for Immunotherapy of Cancer and a faculty member at Massachusetts General Hospital in Boston. “We can get isolated laboratory abnormalities, such as anemia. A lot of patients don’t want to [report problems] because they don’t want to go off the treatment. But if we can intervene when the side effects are minimal, the likelihood that they will stay on the treatment is higher, so I often have [to explain that to patients]. One thing I can say across the board with all of these side effects is the earlier they are identified and treated, the more rapidly they seem to come under control.”

At the other extreme are patients who recognize they are having symptoms but don’t realize they are side effects of their treatment or misunderstand their implications. “They go to the emergency room and say, ‘I’m on chemotherapy.’ The poor emergency room doctor may [be misled or may] not understand that immunotherapy is really different from chemotherapy,” Kaufman said. Kaufman gives his patients cards explaining about their ICP inhibitor treatment, but not everyone carries them.

Trying to keep treatment going

Selamet said the treatment generally requires stopping the ICP inhibitors for both the glomerular nephritis and AIN: “The problem we have from the oncology side is that the drug is working against the tumor, so we don’t want to stop it. But if it is causing side effects, then we do have to hold it. It is really important to recognize these side effects because if you catch them early and treat them, oftentimes you can restart the ICP inhibitors, and the patient will not get the same side effect again. But if they are incompletely treated or if the patient isn’t diagnosed with the side effect until it is late, then it is much harder to keep them on ICP therapy. And at some point, the damage may not be reversible.”

Often, when the side effects erupt, the immune system causes problems that go well beyond the kidney. There can be damage to the liver, lung, colon, or endocrine organs as well. “When it is more than one organ, you have more than one reason to stop the agent. Like other chemotherapy, when it becomes toxic, you try to change the cancer treatment,” Selamet said.

In some cases, when patients are convinced the immunotherapy is needed to save their lives, they may decide that the side effects are worth the cost, and thus may progress to dialysis.

The need for clinicians to be familiar with immunotherapy agents and their side effects will only grow as more of them come on the market and the indications for their use expand. The currently approved agents are in a wide range of clinical trials and many others are in development. The first agents were approved in 2012, and their effectiveness has only increased researchers’ enthusiasm about their potential.

“We think now that the immune system is really capable of mediating anti-tumor activity against almost any type of tumor,” Kaufman said. “There are some types that have been holdouts that haven’t responded and we are trying to understand why that is the case. We think eventually most cancers might be amenable to at least some form of immunotherapy.” ■

Figure 1. Immune checkpoint inhibitors’ mechanism of action

