Kidney Toxicities Associated With Novel Cancer Therapies

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Targeted therapies that act via unique molecular pathways and interfere with cancer cell growth and tumor progression have dramatically changed the cancer treatment paradigm. However, although, ideally, these therapies intend to target only cancer cells, they do often affect nonmalignant tissue. Numerous renal side effects have been reported to date. This article will review clinical presentation, presumed pathophysiology, and treatment of kidney side effects of targeted therapies. Feasibility of the continuation of cancer therapy despite renal toxicity will also be addressed.

Key Words: Targeted therapy, Kidney toxicity, Acute kidney failure, Immunotherapy, Anti-angiogenic therapy

INTRODUCTION

As of January 2016, there were 15.5 million patients alive with a history of cancer in the United States. It is estimated that the population of cancer survivors will increase to 20.3 million into the next decade.[1] This field of medicine is rapidly growing with the recent development of multiple new therapies effective against advanced cancers. Many of these new therapies have potential for nephrotoxicity that practicing nephrologists should be aware of. Patients with malignancies have seen their prognosis and life expectancy improved in recent years, and cancer now in many cases is a chronic disease. Consequently, kidney adverse effects from cancer therapies can have impact on the quality of life and the survival of these patients. This article intends to review clinical presentation and management of kidney adverse effects of many recently developed cancer treatments (Table 1).

IMMUNE CHECKPOINT INHIBITORS

The immune system plays an important role in the development and progression of malignancies. Monoclonal antibodies directed against immune checkpoints can significantly change the prognosis of a variety of cancers. These agents block the inhibitory immune signals, improving the immune system's activity against tumor cells. One class of antibodies targets cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and the other targets the programmed cell death protein 1 (PD-1) and its ligand (PD-L1).[2] When T-cell lymphocytes are activated, CTLA-4 is upregulated on the cell membrane. PD-1 is also expressed on activated T cells and binds both PD-L1 and PD-L2. CTLA-4 and PD-L1 interact with B7 to block co-stimulation and suppress T-cell function. PD-L1 is also expressed on many tumor cells.[2] Ipilimumab and tremelimumab are antibodies that target CTLA-4. Nivolumab, pembrolizumab, and pidilizumab act against PD-1.[2] Finally, atezolizumab and avelumab target PD-L1, the latter still being in clinical development.[3,4]

Immune checkpoint inhibitors have significantly improved survival for advanced melanoma, kidney cell carcinoma, non-small cell lung cancer (NSCLC), urothelial carcinoma, and head and neck cancer.[5] However, these agents are associated with immune-related adverse effects (IRAE). Dermatologic complications are the most common IRAE, but colitis, hepatitis, pneumonitis, thyroiditis, and hypophysitis have also been reported.[6] Immune-related adverse effects may be less severe and less frequent with PD-1 inhibitors compared with CTLA-4 inhibitors.[7]

Lately, they have also been associated with autoimmune kidney adverse effects. Multiples cases reports link anti-CTLA-4 and anti-PD-1 inhibitors to biopsy-proved acute interstitial nephritis (Fig 1).[8-11] Over the 3695 patients enrolled in clinical trials for immunotherapy, 2.2% developed acute kidney injury (AKI). The risk increases with combination of CTLA-4 and PD-1 inhibitors with an incidence of AKI of 4.9%.[12] Patients usually presented with acute rise in serum creatinine, sterile pyuria, mild tubular proteinuria, and occasionally rash, fever, and eosinophilia.[9] The median time from starting the treatment to the kidney failure is approximately 3 months, but it can vary from 1 to 8 months.[12] In a series of 13 cases of AKI secondary to checkpoint inhibitors, 4 patients required kidney replacement therapy and 6 patients already had IRAE not involving the kidney before developing AKI. One patient had evidence of thrombotic microangiopathy on the biopsy and the 12 other patients had pathologic features of AIN with 3 of them having granulomatous AIN.[12]

Because IRAE are largely autoimmune phenomena, a variety of immunosuppressive agents have been used to treat them. Currently, treatment options are based on expert opinions and case series.[7] The half-life of nivolumab is related to the dose and varies from 12 to 20 days. In contrast, PD-1 occupancy on the cell surface is dose independent. Two months after drug infusion, even when serum concentration is undetectable, >70% of PD-1 receptors are still bound to the antibodies.[7] In the case series

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from Cortazar and colleagues,[12] all patients with AIN had partial or complete response to steroid therapy. Steroids were generally tapered over at least 12 weeks.

Although, to date, most published reports associate immunotherapy with tubular toxicity, there are several recent case reports of nephrotic syndrome in setting of PD-1 and CTLA-4 therapy. Glomerular lesions vary with focal segmental sclerosis, membranous nephropathy, and minimal change disease reported.[13-15]

Because immune checkpoint inhibitors block the negative feedback of the immune system leading to brisk immune responses, their safety in transplant patients has been questioned. Lipson and others[16] described 2 patients with kidney transplantation who received ipilimumab without acute rejection. However, 4 case reports of acute allograft rejection secondary to anti-PD-1 antibodies have been reported.[17-20] In all these cases, patients had significant reduction of their tumor burden at the expense of returning to chronic dialysis. The risk of rejection seems to be higher with anti-PD-1 compared with anti-CTLA-4, suggesting that the PD-1 pathway is more important for kidney allograft tolerance. However, one recent report details successful treatment of malignancy with PD-1 inhibitor in the kidney transplant patient with concurrent administration of immunosuppressive regimen of steroids and sirolimus.[21]

CLINICAL SUMMARY

- Novel targeted cancer therapies are associated with a variety of kidney complication, for example-Immune check point inhibitors cause activation of innate immune system leading to acute interstitial nephritis.
- Proteinuria, hypertension, and, in more severe cases, thrombotic microangiopathy have been associated with antiangiogenic therapies.
- Epithelial growth factor pathway inhibition may lead to hypomagnesemia due to decreased renal distal reabsorption.
- In selected patients, it is feasible to continue targeted therapies despite the development of adverse kidney reactions, and in most patients, the side effects resolve after withdrawal of the offending agent.

VEGF INHIBITORS

Angiogenesis is essential to provide nutrients and oxygen to neoplastic cells. Vascular endothelial growth factor (VEGF) is a proangiogenic factor that binds to a family of VEGF receptors (VEGFR), with tyrosine kinase activity.[22] Several classes of antiangiogenic therapies targeting VEGF pathway are now approved to treat different types of neoplasia. Bevacizumab is a humanized monoclonal antibody that blocks VEGF-A. Ramucirumab is a recombinant human monoclonal antibody directed against VEGFR-2. Another group of agents targeting angiogenesis are small molecule multitarget tyrosine kinase inhibitors (TKI). Sunitinib, sorafenib, axitinib, and others are TKI currently in clinical use. Finally, aflibercept is a VEGF trap, a soluble protein that binds to VEGF and inhibits its action.

VEGF inhibitors have multiple kidney adverse effects. They can cause isolated proteinuria, nephrotic syndrome, hypertension, thrombotic microangiopathy, and acute interstitial nephritis. In the kidneys, VEGF is expressed in podocytes and is necessary for adequate function of glomerular endothelium.[23] VEGF pathway inhibition can cause hypertension, but the mechanism is not completely understood. VEGF is a mediator of endothelium-dependent vasorelaxation and cause upregulation of endothelial nitric oxide synthase. There may also be a role of capillary rarefaction, increased production of prostacyclin, and a possibility that VEGF inhibition exacerbates high salt intake hypertension.[22]

In a meta-analysis of 1850 patients treated with bevacizumab, 16% of patients in the high-dose group and 8.7% of patients in the low-dose group developed grade III hypertension with a blood pressure of at least 150/100 or requiring at least 2 drugs to control hypertension.[24] In another meta-analysis of 4609 patients treated with sunitinib, the incidence of all-grade hypertension was 21% and the incidence was significantly higher in patient with kidney cell carcinoma.[25] The use of aflibercept is associated with an increased risk of developing hypertension compared with bevacizumab.[26]

The development of hypertension after treatment with antiangiogenic therapy may be a biomarker of response to therapy. Several recent studies showed an association between development of hypertension and improved progression-free survival and overall survival in cancer patients treated with antiangiogenic therapy.[27-29] Titration of the dose of antiangiogenic therapy with hypertension as a target can enhance the response to treatment.[30] Currently, there is limited data on blood pressure control in oncologic patients. Therefore, the management of these hypertensive patients is not different from the general population in JNC 8 guidelines.[31] Patients with cancer have a limited life expectancy, but hypertension, when it is severe, can lead to serious complication short term. Because anti-VEGF therapy prolongs life expectancy, management of cardiovascular co-morbidities can have an impact on overall survival. Given that hypertension may be associated with a better response to treatment, patients on antiangiogenic therapy should be managed with anti-hypertensive drugs, and chemotherapy treatment should be maintained whenever possible. Pre-existing hypertension should be controlled before initiation of VEGF therapy. Hypertension should not be managed too aggressively because cancer patients are prone to hypotension secondary to hypovolemia or sepsis. Finally, hypertension usually occurs rapidly after the first cycle of VEGF inhibitors and resolves with cessation of treatment.[25]

Because angiotensin II increases VEGF expression and promotes angiogenesis, RAS blockade may have antitumor effect.[32,33] In a retrospective study of 4736 patients with metastatic kidney cell carcinoma, the use of angiotensin system inhibitors in patient on VEGF inhibitors was associated with an increased overall