REVIEW ARTICLE

Immune checkpoint inhibitor (ICPI) induced Nephrotoxicity An Insight

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There has been a marked increase in the therapeutic armamentarium of antineoplastic medications. Various classes of drugs acting at different sites have been developed over decades with the immune system being the latest target[1]. The ability of the immune system to inhibit the cancerous growth of cells is called cancer immune-surveillance. Immune cells, primarily lymphocytes, recognize, and eliminate cells with spontaneous or inherited mutations that encourage malignant transformation [1,2].

The immune system acts in three phases to perform immune-surveillance. The **first phase** is the **elimination phase** in which the immune system eliminates transformed tumor cells before they become clinically evident. The **second phase** is the **equilibrium phase where** the tumor cells that survive the first phase are kept in check and prevented to proliferate further. The **third phase** is an **escape phase** in which tumor cells overcome immune defenses by loss of tumor antigens leading to a reduced recognition of tumor cells or by activation of immune checkpoint molecules such as cytotoxic T Lymphocyte antigen (CTLA-4) and programmed cell death protein 1 (PD-1). These checkpoints help keep immune responses from being too strong and sometimes can keep T cells from killing cancer cells [1].

Immune checkpoint inhibitors (ICPIs) may be defined as a drug that blocks checkpoints. When these checkpoints are blocked, T cells can better kill cancer cells. ICPIs resist cancer evasive mechanisms by allowing host immune cells to identify and eliminate malignant cells [1,2].

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Pharmacologically, ICPIs are monoclonal antibodies targeting inhibitory receptors on T cells, tumor cells, and many other immune cells. Receptors including CTLA-4, PD-1, and PD-ligand 1 (PD-L1) are inhibited, activating T cells for antitumor activity [1,2]. ICPIs currently in use are mentioned in Table 1. ICPIs are increasingly being used in patients with melanoma, non-small cell lung cancer, urothelial cancer, renal cell carcinoma and many other malignancies [3,4].

Table 1. Various classes of ICPIs available.

CLASS	DRUG
anti-CTLA-4 antibodies	Ipilimumab, Tremelimumab
anti- PD-1 antibodies	Nivolumab, Pembrolizumab, Cemiplimab, Spartalizumab
anti-PD L1 antibodies	Atezolizumab, Avelumab, Durvalumab, Pidilizumab.

Various side effects have been reported with ICPIs. In this review, we will be briefing about these side effects with emphasis on thenephrotoxic potential of ICPIs and their use in dialysis and renal transplant patients.

Immune-related adverse effects

Immune-related adverse events have been reported in >50%

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of patients being treated with ICPIs with 20% of patients developing severe (grade 3) or life-threatening (grade 4) toxicities. Commonly affected organs are skin, gastrointestinal tract, liver, and endocrine organs. Commonly reported GI complications to include diarrhea, colitis, hepatitis, and constipation. Skin involvement includes rash, pruritus, eczema, sweet's syndrome, psoriasis Vulgaris, alopecia, and lichen planus. Endocrine side effects include hypophysitis, diabetes mellitus, pancreatitis, hypothyroidism, thyroiditis. Cardiac side effects reported are arrhythmia, pericarditis with effusion, cardiac tamponade, myocardial fibrosis, conduction blocks, troponin elevation, and myocarditis. Radiculitis, generalized epileptic seizures, aseptic meningitis, and myasthenia gravis have also been reported [5,6].

Nephrotoxicity

There are various forms of nephrotoxicity reported with ICPIs[7,8]. From the asymptomatic rise in creatinine to active urinary sediment, proteinuria, hematuria, oliguria, all have been reported. Various kidney lesions have been documented in the setting of ICPIs therapy. The most common lesion described is acute interstitial nephritis(AIN), one-quarter of these lesions have associated granulomas[9]. Less commonly acute tubular necrosis(ATN), glomerulonephritis, and thrombotic microangiopathy has been reported [10,11].

Acute Kidney Injury (AKI)

First described in 2014, two patients on Ipilimumab, reported having granulomatous AIN[11]. Six cases of AKI were reported in 2016 with biopsy-proven AIN following treatment with Nivolumab and Pembrolizumab[12]. In another report, 13 patients developed AKI following exposure to ICPIs, AIN documented in 12, and granulomas in 3 of them. One patient had thrombotic microangiopathy. The overall incidence of ICPI-AKI is 2 to 3% based on data from various studies, reaching up to 5% in patients on combination ICPI therapy[13]. ICPI-AKI diagnosis is based on clinical features alone, and in some cases confirmed by kidney biopsy[14,15].

The National Cancer Institute defines AKI, by comparing changes in serum creatinine to the upper limit of normal. Kidney Diseases Improving Global Outcomes (KDIGO) defines AKI according to relative changes in AKI (Table 2). Another definition and classification system has been proposed (Table 3)[8]. Severe AKI defined as an increase in serum creatinine more than threefold above baseline, an increase in serum creatinine to >4 mg/dl, or need of dialysis, was 0.6%[13].

Table 2. Grading system for ICPI associated AKI

SYSTEM	GRADE	DESCRIPTION
CTCAE	Grade 1	Higher than ULN to 1.5× ULN
	Grade 2	> 1.5-3.0 × baseline; 1.5-3.0 × ULN
	Grade 3	3.0 × baseline; > 3.0 - 6.0 ×ULN. Hospitalization indicated
	Grade 4	>6.0 × ULN; life -threatening consequences; RRT indicated
	Grade 5	Death
KDIGO	Stage 1	Increase in SCr of ≥0.3 mg/dl within 48 hrs or 1.5-1.9 × baseline
	Stage 2	Increase in SCr to 2-2.9 × baseline
	Stage3	Increase in SCr to 3 × baseline s or to ≥4.0mg/dl or initiation of RRT

CTCAE, Common Terminology Criteria for Adverse Events; ULN, Upper Limit of normal

Table 3. Definition and classification of ICPI -associated AKI

Classification	Definition
Definite ICPI-AKI	Kidney biopsy confirmed diagnosis compatible with ICPI-AKI and after clinical review of risk factors
Probable ICPI - AKI	BOTH of the following Sustained ↑ in SCr ≥50% on at least two consecutive values or need for RRT. Absence of an alternative plausible etiology AND at least one of the following Sterile pyuria (≥5 WBCs/hpf) Concomitant or recent extra renal irAE eosinophilia(≥500 cells/µl)
Possible ICPI-AKI	BOTH of the following ↑ inSCr ≥50% or need for RRT. AKI is not readily attributable to alternative causes

ICPI-AKI, immune checkpoint inhibitor-associated AKI, irAE, immune-related adverse event

Risk factors include prior or concomitant proton pump inhibitor use, prior or concomitant extra-renal irAEs.

Most patients present with rising creatinine, sterile pyuria, or sub nephrotic proteinuria. Eosinophilia is found in a minority of patients. After initiation of ICPIs median time to AKI is 14 weeks, much delayed in comparison to extra-renal side effects that appear within 4 weeks. Risk factors for developing AKI include concomitant use of proton pump inhibitors, combination treatment with anti-CTLA-4 and anti-PD-1/PD-L1 agents, and lower baseline GFR[8,12,13].

Patients who present with stage1 AKI should be evaluated for reversible causes like dehydration, hypercalcemia, urinary obstruction, or other nephrotoxic drug exposure.

Patients with persistent stage1 and stage 2 or 3 AKI should undergo kidney biopsy. Empirical treatment with steroids should be considered only if there is a contraindication to performing kidney biopsy with an absence of alternative etiology for AKI [8].

Glucocorticoids are the mainstay of treatment of ICPI induced tubulointerstitial nephritis, backed by observational data. The commonly used protocol is prednisolone 1mg/kg daily with a slow taper over 2-3 months. In patients with severe AKI, intravenous methylprednisolone 250-500 mg daily for 3 days may be used as initial therapy. Other agents used particularly in steroid-resistant patients include mycophenolate mofetil, cyclophosphamide, rituximab, and infliximab [8,13].

Usually, ICPI is withheld in patients with severe AKI. However, patients who have exhausted other options for chemotherapy may need to be rechallenged with ICPIs. In patients who develop grade 3 or higher AKI, ICPIs should be permanently discontinued according to the American Society of Clinical Oncology guidelines. But in one multicenter study thirty-one patients were rechallenged and only seven (23%) developed recurrent AKI, six of them showed partial or complete recovery. Rechallenge may be attempted in patients who have shown tumor response after a renal injury has resolved or stabilized[8].

Glomerular disease. Nephrotic syndrome was first reported in a patient with metastatic melanoma, following ipilimumab treatment. Kidney biopsy revealed minimal change disease with complete foot process effacement. Complete resolution of proteinuria was achieved after discontinuation of ipilimumab and glucocorticoid treatment[14]. Collapsing Focal Segmental Glomerular Sclerosis(FSGS), with AKI has been reported following exposure to nivolumab, with no improvement after drug withdrawal and glucocorticoid treatment[15]. One patient with FSGS has been reported, with no improvement in drug withdrawal and glucocorticoid treatment, improved with mycophenolate mofetil[16]. Immune complex GN has been reported on exposure to ICPIs, including ipilimumab associated lupus-like glomerulopathy. Phospholipase A2 receptor antibody-negative membranous nephropathy has been reported in a patient on nivolumab, achieving partial recovery after the withdrawal of drug and glucocorticoid therapy[17].

ICPIs in End-Stage Renal Disease(ESRD)

Experience of using ICPIS in ESRD is limited to case reports and small case series[18,19]. A total of 26 patients, mostly on hemodialysis have been described in the literature[20]. Ipilimumab, Nivolumab, Pembrolizumab, and Atezolizumab have been used in treating ESRD patients, for various malignancies including melanoma, renal cell carcinoma, squamous cell skin carcinoma, urothelial cancer, and non-small cell lung cancer. ICPIs are not renally excreted, so dose modification is not needed. Immune-related adverse events are similar to non-ESRD patients[19,20].

ICPIs in Kidney Transplant patients

Immunosuppressive drugs used in post-renal transplant patients predispose to cancer by inhibiting immune surveillance, suppressing DNA repair, and predisposing to oncogenic viral infections[21,22]. Due to an increased predisposition to rejection with the use of ICPIs, transplant patients have been excluded from clinical trials of ICPIs. The use of ICPIs has been anecdotal[23,24,25]. It has been observed that the rejection rate with Ipilimumab monotherapy was 33% compared to 52% with anti-PD-1 monotherapy and 55% with combination therapy[29]. The strategies to prevent the high rate of rejection include the use of pre-emptive steroids and mammalian target of rapamycin (mTOR) inhibitors. Alternatively, calcineurin inhibitors may be continued during ICPI use. Depending upon the individual immunological risk, a decision about reduction or interruption of immunosuppression must be balanced with a high risk of rejection with ICPICs [26].

With ICPIs as the new class of antineoplastic medications, it is important that the oncologist, physicians, and the nephrologists be aware of various toxicities as well as its management.

REFERENCES

1. Leach DR, Krummel MF, Allison JP: Enhancement of antitumor immunity by CTLA-4 blockade. Science 1996; 271: 1734-1736.
2. Boussiotis VA.Molecular and biochemical aspects of the PD-1 checkpoint pathway. N Engl J Med 2016; 375: 1767-1778.
3. Callahan MK, Kluger H, Postow MA, Segal NH, Lesokhin A, Atkins MB, et al.Nivolumab plus ipilimumab in patients with advanced melanoma: updated survival, response, and safety data in a phase 1

dose-escalation study. J ClinOncol 2018; 36:391-398.

4. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP et al; KEYNOTE-001 Investigators: Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015; 372: 20182028.
5. Postow MA, Sidlow R, Hellmann MD: Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018; 378: 158168
6. Sury K, Perazella MA, Shirali AC: Cardiorenal complications of immune checkpoint inhibitors. Nat Rev Nephrol 2018; 14: 571588.
7. Perazella MA, Shirali AC: Nephrotoxicity of cancer immunotherapies: Past, present and future. J Am SocNephrol 2018; 29: 20392052.
8. Shruti Gupta, Frank B. Cortazar, Leonardo V. Riella, David E. Leaf. Immune Checkpoint Inhibitor Nephrotoxicity: Update 2020. Kidney 2020; 360: 130-140
9. Shirali, A. C, Perazella, M. A. &Gettinger, S. Association of acute interstitial nephritis with programmed cell death 1 inhibitor therapy in lung cancer patients. Am. J. Kidney Dis 2016; 68:287291.
10. Cortazar, F. B. et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. Kidney Int 2016; 90, 638647.
11. Izzedine, H. Kidney injuries related to Ipilimumab. Invest New Drugs 2014; 32: 769773.
12. Izzedine H, Mathian A, Champiat S, Picard C, Mateus C, Routier E, et al : Renal toxicities associated with pembrolizumab. Clin Kidney J 2019; 12: 8188.
13. Seethapathy H, Zhao S, Chute DF, Zubiri L, Oppong Y, Strohbehn I et al: The incidence, causes, and risk factors of acute kidney injury in patients receiving immune checkpoint inhibitors. Clin J Am SocNephrol 14: 16921700, 2019
14. Kidd, J. M,Gizaw, A. B. Ipilimumab-associated minimal-change disease. Kidney Int 2016;. 89, 720
15. Ray, A., Ghosh, S., Ghosh, M. &Yarlagadda, S. Nivolumab induced renal failure with collapsing focal segmental glomerulosclerosis (FSGS). J. Am. Soc. Nephrol 2016; 27, 1010A.
16. Daanen, R. A. et al. Nivolumab-associated nephrotic syndrome in a patient with renal cell carcinoma: a case report. J. Immunother 2017. 40, 345348.
17. Lin, J., Schiff, M., Salvatore, S., Shoustari, A. &Glezerman, I. Membranous nephropathy related to the checkpoint inhibitor nivolumab. J. Am. Soc. Nephrol 2016; 27, 102A.
18. Cheun H, Kim M, Lee H, OhK-H, Keam B. Safety and efficacy of immune checkpoint inhibitors for end-stage renal disease patients undergoing dialysis: A retrospective case series and literature review. Invest New Drugs 2019; 37: 579583.
19. Vitale MG, Baldessari C, Milella M, Buti S, Militello AM, Di Girolamo S et al. Immunotherapy in dialysis-dependent cancer patients: Our experience in patients with metastatic renal cell carcinoma and a review of the literature. ClinGenitourin Cancer 17: e903e908, 2019
20. Jamie S. Hirsch, RimdaWanchoo, Jia H. Ng, YurilyKhanin, and Kenar D. Jhaveri. Use of Immune Checkpoint Inhibitors in End Stage Kidney Disease Patients, Single Centre Experience and Review of Literature: Kidney 2020; 360 1:399-402.
21. Sprangers B, Nair V, Launay-Vacher V, Riella LV, Jhaveri KD: Risk factors associated with post-kidney transplant malignancies. Clin Kidney J 11: 315329, 2018
22. Hurkmans DP, Verhoeven JGHP, de Leur K, Boer K, Joosse A, Baan CC et al. Donor-derived cell-free DNA detects kidney transplant rejection during nivolumab treatment. J Immunother Cancer 2019; 7: 182.
23. Boils CL, Aljadir DN, Cantafio AW: Use of the PD-1 pathway inhibitor nivolumab in a renal transplant patient with malignancy. Am J Transplant 2016; 16: 24962497.
24. Spain L, Higgins R, Gopalakrishnan K, Turajlic S, Gore M, Larkin J: Acute renal allograft rejection after immune checkpoint inhibitor therapy for metastatic melanoma. Ann Oncol 2016; 27: 11351137.
25. Barnett R, Barta VS, Jhaveri KD: Preserved renal-allograft function and the PD-1 pathway inhibitor nivolumab. N Engl J Med 2017; 376: 191192.
26. Venkatachalam K, Malone AF, Heady B, Delos Santos R, Alhamad T: Poor outcomes with the use of checkpoint inhibitors in kidney transplant recipients. Transplantation 2020; 104(5):1041-1047