Renal Toxicity

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Abstract

With the increasing use of immunotherapy, there has been an associated increased survival in many cancers but has also resulted in unregulated organ-specific toxicities. In this chapter, we discuss the renal toxicities associated with a checkpoint inhibitor (CPI) from the typical acute tubulointersitial nephritis to glomerulonephritis, their proposed mechanisms, and treatments. We also discuss the use of CPI and reactivation of preexisting autoimmune diseases and focus on renal cell cancer in setting of Chronic kidney disease (CKD). Transplant rejection in the setting of CPI use is yet to be further studied, and available data is presented in this chapter.

Keywords

Acute interstitial nephritis · Autoimmune disease induction · Organ transplant rejection · Renal cell cancer · Immune-related adverse events

Introduction

With the advent of the era of immunotherapy, there has been a marked increase in survival in several cancers, such as advanced melanoma, renal cell carcinoma, non-small cell lung cancer (NSCLC), urothelial carcinoma, and head and neck cancers. Harnessing the immune system against tumor by releasing the breaks off the regulators of the immune system, such as 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), has also resulted in unregulated organ-specific toxicities. The expansion in the use of checkpoint inhibitors has gained great momentum, being used in solid tumors to hematological malignancies and widely tested in clinical trial. The recognition of increasing adverse events associated with checkpoint inhibitors has created the terminology immune-related adverse events (IRAEs). The adverse events have been associated with poorer survival outcomes [1]. Autoimmune colitis, hepatitis, endocrinopathies, and cutaneous IRAEs were the most frequently reported adverse irAEs, with renal toxicity comprising 3.8%, based on a meta-analysis evaluating case reports [1]. A study by Cortazar et al. looked at the incidence of acute

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kidney injury (AKI) in 3695 patients on clinical trials treated with a checkpoint inhibitor (CPI); the overall incidence of AKI was 2.2%. The incidence of grade III or IV AKI and need for dialysis was 0.6% [2]. AKI occurred more frequently in patients who received combination therapy with ipilimumab and nivolumab (4.9%) than in patients who received mono-therapy with ipilimumab (2.0%), nivolumab (1.9%), or pembrolizumab (1.4%) [2]. When defining AKI based on AKI network criteria in a population of 99 patients, incidence of AKI was reported to be a low as 9.9% and as high as 29% [3]. In this chapter, we address renal toxicity associated with checkpoint inhibitors and its implication on the development of chronic kidney diseases, which can affect the overall survival, especially, in renal cell carcinoma patients.

Renal Toxicity AIN

The most commonly associated renal toxicity with CPI has been acute interstitial nephritis (AIN), with some reports of granulomatous interstitial nephritis [2, 4–6]. AKI has been noted to occur from 1 to 8 months, with a reported median time of 3 months for development since starting treatment [2]. Patients often present pyuria, subnephrotic proteinuria, with rare cases of eosinophilia, rash, or fevers, which are typical of AIN [7]. Since CTLA-4 activity is in the lymphoid organs regulating peripheral tolerance, it has been demonstrated in CTLA-4-deficient mice, a lymphoproliferative disease develops with multiorgan lymphocytic infiltration and tissue destruction [8, 9]. PD-1 regulates tolerance primarily at the level of target organs. In mice models PD-1, PD-L1 are important inhibitory regulators of CD8(+) T cells in tubulo-interstitial inflammation and provide protection from ischemic reperfusion injury [10, 11]. The mechanism associated with CPI and renal injury is yet to be elucidated; however, what has become evident is the delayed response after exposure to CPI, which is not typical of AIN. It has been suggested that due to the disruption of CTLA-4 and PD-1 signaling, there is loss of self-tolerance and leads to migration of autoreactive T cells to the kidney, leading to a significant inflammatory response with a predominance of T cells. There have been further studies indicating PD-L1 acts as a protective molecule against CD8+ CTL activation in renal parenchymal immune [12], which would support a possible mechanism where the activated T cells against possible drugs such as antibiotics and proton pump inhibitors are no longer exhausted when you inhibit PD-1 and therefore mount an immune response [4, 13]. The presence of autoreactive T cells that have escaped the negative selection process in the thymus could also potentially be activated in the presence of CPI and lead to tissue inflammation [14, 15].

Auto-Immune Induction and Preexisting Auto-Immune Disease

Interestingly, IRAE has included induction of autoimmune diseases after use of CPI such as sarcoidosis, lupus, psoriasis, diabetes, and polymyalgia rheumatic/arteritis, among others. Not all patients develop autoimmune diseases but likely the ones with genetic predisposition and nongenetic or environmental factors, such as infections, vitamin D level, smoking, microbiota, and changes in the T-cell receptor repertoire [16, 17]. A possible mechanism is that the treatment with CPIs may result in the unveiling of underlying "silent" autoimmunity, resulting in chronic, persistent inflammatory disease that is treated as a primary autoimmune disease [18]. Rheumatologists have appreciated the autoimmune induction post CPI and have advocated for questionnaires for patients on CPI and autoimmune serology screening [19]. Autoimmune diseases have not escaped the kidney: there have been case reports of lupus nephritis, minimal change disease, and thrombotic microangopathy after CTLA-4 antibodies treatment [20, 21]. Interestingly, there is evidence that PD-1 is involved in autoimmune diseases as demonstrated in PD-1 knock-out mice models who develop lupus and severe arthritis [22]. A recent abstract has reported on membranous

nephropathy, ANCA vasculitis, IgA nephropathy, C3 glomerulopathy, AA type amyloid, and the typical AIN after CPI [23]. One of the cases in the series with AIN had aggressive T cell infiltration, with CD4+ and CD8+ T cell infiltration, and further demonstrated in another case in the literature [15, 23]. The glomerulonephritis (GN) noted in these biopsies presented with either CTLA-4 antibodies or PD-1 inhibitors treatments [23]. Patients with GN after CPI have been treated as de novo GN with some success. Another interesting notion is the higher likelihood of patients with preexisting autoimmune disorders to develop irAE on CPI. There are limited data available about management of these patients. In a recent met-analysis by Abdel-Wahab et al., among 123 patients, 92 (75%) had irAEs, of which 50 patients (41%) had exacerbation of their current autoimmune symptoms, 31 (25%) had new irAEs, and 11 (9%) had both. Interestingly, two cases had preexisting autoimmune nephritis (IgA nephropathy and IgM nephropathy) [24]. In a prospective study of 45 patients with cancer and preexisting autoimmune or inflammatory disease, treatment with anti-PD-1 antibodies demonstrated that patients with preexisting autoimmune disease were more likely to have irAE. Overall survival in the group with autoimmune disease versus the group without was no different [25].

Kidney Transplant and CPI

There is an increased incidence of melanoma of 2.4 times higher in solid organ recipients compared to the general population, with renal or liver transplant recipients having a higher risk [26]. Treatment protocols and management of possible organ rejection is an *unmet* need especially in kidney transplant patients. This has been highlighted in published case reports. Cases by Lipson et al. initially reported successful treatment of melanoma in kidney transplant patients using ipilumumab; however, more recently, cases of acute rejection were published [27, 28]. More cases have displayed the prevalence of increased risk of rejection of organs after CPI treatments. Based on publications, there were six cases of kidney transplant patients who underwent CPI treatment, with four patients developing rejection, leading to the conclusion that the patients treated with PD-1 inhibitors and combination therapy of ipilimumab and PD-inhibitors were more likely to develop rejection [29–31]. PD-1 and PD-L1 interactions might participate in the induction of allograft tolerance. PD-L1 can limit effector T cell function and expansion as well as induce regulatory T cells, allowing for increased graft tolerance. There is also evidence of upregulation of PD-1 on T cells and PD-L1 on hematopoietic and organ transplant cells, which limits allo-specific T cell activation and proliferation against the allograft [32, 33]. Using PD-1 as a target for therapeutic strategy to improve graft survival has been further investigated by enhancing the expression of PD-1 or PD-L1 [34].

A recent comprehensive review work further supports that PD-1 antibodies may be more likely to lead to rejection. In a recent study by Abdel-Wahab et al., 39 patients with allograft transplant were identified from both institutional and literature review of case reports. Fifty-nine percent had prior renal transplantation with a median time to CPI initiation after solid organ transplant (SOT) was 9 years (range 0.92–32 years). Allograft rejection occurred in 41%. There was no difference in rejection rates in anti-CTLA-4 and anti-PD-1. Median time to rejection was 21 days (95% confidence interval (CI):19.3–22.8 days). There were no associations between frequency, timing, or type of rejection and time interval since SOT. Graft loss occurred in 81%. Death was reported in 46% [35, 36].

Renal Toxicity in RCC

Chronic kidney disease (CKD) and cancer have a bidirectional relationship. This is evident in the observations that cancer and/or its treatments can lead to CKD and that CKD is a risk factor for cancer development. A number of observational studies have shown the high prevalence of CKD in patients with solid tumors [37–40]. RCC account for 2.4% of adult malignancies, the vast

majority being clear cell histology:ccRCC [41]. Evaluating data from the Fox Chase Cancer Center, Canter et al. [42] showed that 22% of 1114 RCC patients had CKD stage 3 or higher before nephrectomy, and this percentage increased to 40% for patients older than 70 years [42]. Therefore, many patients with RCC are likely to have CKD before the use of systemic therapy. Two decades ago, the initial treatments for RCC involved targeting the immune system using interleukin 2 (IL-2) and interferon alpha (IFN-α). Following the VHL/HIF/VEGF underlying biology understanding, targeted therapies such as anti-vascular endothelial growth factor (VEGF), tyrosine kinase inhibitors (TKIs), and mTOR inhibitors became the mainstay treatments with clear benefit in progression-free survival [43]. These VEGR TKI have long been associated with renal toxicity.

PD-L1 is expressed in about 20–25% of ccRCC tumor cells and was independently associated with metastatic cancer progression (RR, 3.46; $P < 0.001$) and death from RCC (RR, 4.13; $P < 0.001$) [44]. RCC patients with tumor PD-L1 expression are at significant risk of rapid cancer progression and accelerated rates of mortality. Clinical trials using Nivolumab in metastatic ccRCC was the first of its class to be approved for the treatment of metastatic, in 2014, after randomized, open-label, phase 3 study compared nivolumab with everolimus (CheckMate 025 study) in patients who had failed prior VEGF inhibition. The median overall survival was 25.0 months with nivolumab and 19.6 months with everolimus (HR 0.73; 98.5%CI [0.57–0.93], $p = 0.0018$) [45]. In CheckMate 025, Motzer et al. reported 8% of the RCC patients had an elevation in creatinine and reported as grade 3 or 4 toxicity [45, 46].

More recently, in first-line setting, the doublet ipilimumab plus nivolumab further demonstrated improved overall survival benefit over standard-of-care sunitinib in the intermediate and poor-risk population. Median OS was not reached for the immuno-oncology combination (95% CI [28.2-NR]) versus 26 months for sunitinib (95% CI [22-NR]) (HR 0.63, 99.8%CI [0.44–0.89]) [47]. Data of renal toxicity specifically are not available yet. Clinical trials are now investigating using combination therapy of anti-VEGF and IO based on high response rate with combination approach in phase I [48, 49]. These combinations of VEGFR/TKI and PD-1/PD-L1 inhibitor will require a great focus on renal toxicity when phase III will be presented. The first combination of VEGF inhibition plus PD-L1 inhibition to have been reported in phase III, is the IMmotion 151 trial of atezolizumab plus bevacizumab compared with sunitinib in first line setting (Motzer, ASCO GU 2018). The grade 3–4 proteinuria and hypertension rates reported in this study were in line with the use of bevacizumab, and this combination presented a favorable safety profile when compared to sunitinib.

Management of Renal Toxicity

The mainstay treatment for renal toxicity associated with CPI has been steroids, as is typically done with other organ irAEs [50]. However, it has become evident that biomarkers for organ toxicity associated with CPI is much needed to understand novel treatments [51]. For example, Interleukin-17 has been noted to be high in patients treated with ipilimumab [52], and therefore use of infliximab at a dose of 5 mg/kg once every 2 weeks is started in patients that fail to respond to steroids after 3 days [53]. There is yet more to be done in the renal realm, and staining renal tissue for cytokines and T cell subtypes from patients with irAEs would further help understand novel approaches. The basic approach with AKI after CPI-use would be a nephrology consult, lab and urine analysis. Also, a kidney biopsy would be indicated to delineate if the patient has AIN versus a glomerular process, which may require more than steroids. Based on case reports and CKIN (Cancer and Kidney International Network Workgroup on Immune Checkpoint Inhibitors), steroids is the mainstay treatment with AIN, starting at 1 mg/kg and tapering over 1–2 months with a close follow-up [46]. Any glomerular disease present would be treated with steroids and would consider further immunosuppressive agents, such as rituximab or cellcept, based on the renal biopsy pathology. This would be in conjunction of holding the checkpoint inhibitor. Possible rechallenge

would be reasonable if all possible contributors to AIN have been discontinued, such as nonsteroidal anti-inflammatory drugs (NSAIDS) and proton pump inhibitors(PPI). Monitoring creatinine closely every 2 weeks would be important to ensure improvement.

As far as kidney transplant recipients are concerned, there is still lacking data in management and the recommendations are based on case reports. Kidney transplant patients treated with CPIs need to have both an oncologist and transplant nephrologist in close communication for possible organ rejection. Close monitoring of renal function especially after immunosuppression is reduced with the diagnosis of cancer. One case in the literature suggests, switching tacrolimus to sirolimus and a higher dose of steroids may have been of benefit in preventing organ rejection while on immunotherapy [54].

Although there has been a concern in the use of steroids and the hampering of antitumor effects of CPI, it has been demonstrated by Horvat et al. in 298 patients treated with ipilimumab, where 85% has irAE, where one-third required systemic steroids with no impact on survival or time to treatment failure [55].

Conclusion

Given the wide use of CPI across tumor types, physicians should be trained to detect renal complications. The large majority of cases present either with creatinine level impairment of renal parenchyma damage, the most common being acute interstitial nephritis. Prompt identification and management are needed to prevent chronic kidney disease.

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