Renal effects of immune checkpoint inhibitors

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Introduction

The immune system plays a critical role in the control and eradication of cancer cells. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) are two important immune checkpoint; their ligands are CD80/CD86 B7 and programmed cell death ligand 1 (PD-L1), respectively. Following binding of the receptors to their specific ligands, T-cell effectors are downregulated, leading to tumor cell tolerance. On the other hand, the inhibition of these immune checkpoint proteins reestablishes the response of T lymphocytes against cancer cells.

Monoclonal antibodies against PD1 (nivolumab, pembrolizumab), PDL-1(atezolizumab) and CTLA-4(ipilimumab) are currently being used for treatment of advanced stage cancers with unprecedented results in survival data. However, recent studies have shown that Checkpoint Inhibitors (CI)-based combinations caused an increased risk of immune-related adverse events (AEs), such as liver, gastrointestinal, skin and pulmonary toxicities. Other rare AEs that have been reported include uveitis, pancreatitis, neuropathies, pneumonitis, myocarditis and renal disorders. Despite being relatively rare (≤1%), the renal affectation should be emphasized because the prognosis of cancer patients with kidney dysfunction has been previously shown to be poor. Moreover, the incidence of renal related adverse events seems to increase until 5% on CI combined therapy.

Immune-related renal effects of Checkpoint Inhibitors

Two different forms of CI-induced renal diseases have been reported in the literature: acute tubulointerstitial nephritis (AIN) and some cases of immune complex glomerulonephritis.

Acute interstitial nephritis induced by CIs is related to severe inflammatory cell infiltrates. In this line, Cortazar described 13 patients with CI-induced acute kidney injury (AKI). The median time for AKI is variable (21–245 days). Most patients presented with pyuria (8 patients) low-grade proteinuria (median 0.48 g/g; 0.12–0.98 g/g) and median peak serum creatinine of 4.5 mg/dL (3.6–7.3 mg/dL). AIN was observed in 12 patients and glucocorticoid treatment of 10 patients resulted in a complete (2 patients) or partial

(7 patients) recovery of renal function. Four patients required haemodialysis despite treatment with glucocorticoids, of whom only two required chronic dialysis. No improvement in renal function was seen in the remaining two patients with AIN, who did not receive glucocorticoid treatment.

It is believed that cell-mediated immunity is implicated in the mechanism of renal injury. CI may reactivate exhausted drug-specific T cells previously primed by nephritogenic drugs, and consequently, due to loss of tolerance, memory T cells are activated against the drug. In this line, 14 out of the 19 patients reported by Cortazar and Shirali were on drugs associated with AIN (proton pump inhibitors and non-steroidal anti-inflammatory drugs).

Regarding immune –complex glomerulonephritis, one patient was reported with nephrotic syndrome and preserved renal function on treatment with ipilimumab (for melanoma). A renal biopsy revealed lupus-related membranous nephropathy with circulating anti-doublestranded DNA antibodies and glomerular IgG, C3 and C1q deposits. In another report, kidney biopsy revealed IgA nephropathy in a patient who developed proteinuria and a worsening kidney function after treatment with nivolumab for a postoperative recurrence of lung squamous cell carcinoma. After drug withdrawal, proteinuria improved and the deterioration of the patient's
renal function was halted.

Treatment

The current standard of care for drug-induced AIN management includes early identification of this disease (renal biopsy) and prompt discontinuation of the culprit medication. Given the underlying immune mediated damage in this disease, steroids therapy has also been used since 1970. However, there is a lack of high-quality evidence to support this practice. Despite this deficiency, the available evidence supports a potential benefit of early steroid administration on long-term recovery of kidney function.

In relation to check point inhibitors, American and European Oncology guidelines stratifiy patients managements based in the severity of renal dysfunction. In mild dysfunction (grade 1) the physician can continue the treatment under strict monitoring of creatinine values, while promoting hydration and cessation of nephrotoxic drugs. If the renal function has worsened to grade 2–3 renal toxicity, treatment should be postponed until creatinine values decrease to at least grade 1, and a renal biopsy should be performed. Prednisolone 0.5–1 mg/ kg daily should be given. If the renal function has worsened to grade 4 renal toxicity, treatment must be stopped, a renal biopsy performed and methylprednisolone dosed at 1–2 mg/kg daily should be given. Moreover, avoidance or discontinuation of other drugs, those known to induce AIN, should be considered.

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