EDITORIAL COMMENT

Pembrolizumab-related renal toxicities: diagnosis first, treatment later

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ABSTRACT

Checkpoint inhibitors are increasingly used to treat different types of malignancy and have been associated with renal toxicities. In this issue, Izzedine et al. report on the incidence of pembrolizumab-associated renal toxicity in a French single-centre nephrology referral centre. They report an estimated incidence of pembrolizumab-related renal toxicities of 1.77% and most notably the most common histologic lesion was acute tubular injury (not acute tubulo-interstitial nephritis). This study further highlights the importance of performing a thorough nephrological workup including kidney biopsy in patients experiencing renal toxicities while receiving pembrolizumab treatment.

Keywords: checkpoint inhibitors, onconephrology, renal injury

On 1 October 2018, the Nobel Prize in physiology was awarded to James Allison and Tasuku Honjo who developed checkpoint inhibitor (CPI) therapy. In the last decade, CPIs have revolutionized cancer therapy and are increasingly used in the treatment of several types of cancer, including melanoma, renal cell cancer, non-small cell lung cancer and Hodgkin’s lymphoma [1]. By inhibition of negative co-stimulatory signalling through cytotoxic T lymphocyte associated protein 4 (CTLA-4) or programmed cell death protein-1/programmed cell death protein-ligand 1 (PD-1/PD-L1) on T cells, CPIs restore tumour-directed T-cell responses [2] and are able to induce long-lasting responses in a subset of patients receiving these medications. However, this boost in T-cell reactivity is also the cause of the CPI-associated side effect, namely immune-related adverse events (iRAEs) [3]. Currently there are four CPIs approved by the US Food and Drug Administration: two CTLA-4-blocking antibodies (ipilimumab and tremelimumab) and two PD-1-blocking antibodies (nivolumab and pembrolizumab). Pembrolizumab (KEYTRUDA) is a humanized immunoglobulin G4 kappa monoclonal antibody directed against PD-1. iRAEs associated with CPI are common and occur in >50% of patients, with Grades III and IV toxicities occurring in 20% of patients, and the most frequently affected organ systems are the skin and gastrointestinal tract. It is well established that combination therapy as well as higher doses of CPIs (ipilimumab 10 mg/kg compared with 3 mg/kg) are associated with more frequent and more severe iRAEs. Moreover, CTLA-4 blockade appears to be more frequently associated with iRAEs than PD-1/PD-L1 blockade. The incidence of iRAEs affecting the kidney is considered to be low, although recent data suggest that renal iRAEs are more common than initially appreciated [4]. Different forms of renal toxicities associated with CPI usage have been reported,
for example, acute kidney injury, acute interstitial nephritis and glomerular diseases [5]. Also, as renal toxicities are concerned, a higher incidence and severity have been observed in patients treated with a combination of CPIs and patients treated with anti-CTLA-4. In a recent pooled analysis, the overall incidence of pembrolizumab-associated iRAEs was 74.3%. Interestingly, in this report, no renal toxicities were reported [6].

In this issue of Clinical Kidney Journal, Izzedine et al. [7] report on the incidence of pembrolizumab-associated renal toxicity in a French single-centre nephrology referral centre and report that renal adverse events occur in 1.77% of patients. A renal biopsy was performed in all 12 patients and acute tubular injury was the most common lesion noted. The most common glomerular pathology in this case series was minimal change disease [7]. As treatment is concerned, 10 of 12 patients stopped pembrolizumab and 7 also received steroids. Pembrolizumab was reintroduced in one patient with acute tubulo-interstitial nephritis, resulting in recurrence of acute tubulo-interstitial nephritis. Overall, renal outcome was favourable after discontinuation of pembrolizumab (and a course of steroids) [7].

The incidence of CPI- and pembrolizumab-associated renal iRAEs varies widely in the literature. It is well established that combination therapy leads to a higher incidence of renal complications (4.9%) compared with monotherapy with ipilimumab (2.0%), nivolumab (1.9%) or pembrolizumab (1.4%) [8]. Interestingly, in a recent review by Wanchoo et al. [4], the incidence of renal toxicities associated with the use of CPI was estimated to be in the range of 9.9–29%. Of note, a recent abstract reported an incidence of renal events as high as 13.9% with the use of these agents in routine practice in the USA, being associated with the highest toxicity-induced costs ($8854) [9]. The incidence of 1.77% in this study is thus in line with previous reports. Estimation of the incidence in this study is, however, suboptimal, as only patients who were referred to the nephrology service were included. Thus, most likely, 1.77% is an underestimation of the true incidence of pembrolizumab-associated renal adverse effects.

Renal dysfunction is common in cancer patients, its aetiology diverse and CPI-associated iRAEs are only one of the possible reasons for renal dysfunction [10]. Therefore a careful evaluation is needed in all cancer patients experiencing kidney dysfunction. This study stresses the importance of performing a kidney biopsy to establish a correct diagnosis of patients with renal dysfunction following pembrolizumab treatment. In my personal experience, in patients receiving CPI therapy experiencing renal dysfunction, CPI therapy is currently readily identified as the culprit both by oncologists and nephrologists, and without appropriate evaluation, CPI therapy is discontinued and steroid therapy initiated. In my opinion, this represents suboptimal clinical practice possibly impeding outcome in these patients. There should be a low threshold to perform a renal biopsy, as this is a safe procedure, although some contraindications exist (solitary kidney, bleeding disorder, anticoagulation treatment that cannot be corrected, horseshoe kidney or other anatomic variants making renal biopsy technically impossible). Performing a kidney biopsy should especially be considered whenever important treatment decisions are made in order to prevent suboptimal cancer treatment due to cessation of CPI and/or initiation of steroids.

In this study, surprisingly, acute tubular injury was the most commonly observed pattern of injury on histology. This is in contrast with other reports that identified acute tubulo-interstitial nephritis as the dominant form of renal injury associated with CPI treatment. A possible explanation is the low threshold to perform a kidney biopsy in this study. The underlying mechanism of pembrolizumab-associated acute tubular injury is unclear and it is not established whether this is also an iRAE or, more likely, related to other non-immunologic factors. This is not only a semantic discussion, but is very relevant to treatment decisions; treatment with steroids is most likely not indicated in patients with acute tubular injury. One could also predict that re-exposure to pembrolizumab is less likely to be associated with a recurrence of renal toxicity in patients with acute tubular injury compared with patients with acute tubulo-interstitial nephritis.

In this study, patients with acute tubular injury were more likely to have cardiovascular risk factors and pronounced vascular lesions on histology, suggesting that an already damaged renal vascular bed predisposes patients to develop tubular injury following pembrolizumab treatment. Future studies are needed to establish risk factors, identify patients at risk and determine outcome and optimal management of patients experiencing acute tubular injury during pembrolizumab treatment.

This study has several limitations: it is a single-centre study; the incidence of pembrolizumab is probably underestimated; given the small numbers, no reliable conclusions can be drawn regarding optimal management, identification of risk factors and outcome and the mechanism of pembrolizumab-associated acute tubular injury is unclear at this time. However, the authors should be applauded for their continuous dedication to improve the knowledge regarding side effects of different anti-cancer therapies. Ideally this study should be complemented by multicentre studies concerning the incidence of CPI-associated renal adverse effects outside the context of studies and consensus guidelines should be developed regarding the optimal diagnosis and management of patients with CPI-associated renal adverse events through a collaboration of oncologists, nephrologists and pharmacologists.

In conclusion, this study identifies renal toxicities as uncommon but possible side effects of pembrolizumab treatment. Given the fact that tubular injury was the predominant lesion noted on renal biopsy, there should be a low threshold to perform a renal biopsy to establish a correct diagnosis before making treatment decisions and provide patients with optimal cancer treatment.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES