Renal toxicities associated with pembrolizumab

Hassan Izzedine, Alexis Mathian, Stephane Champiat, Cécile Picard, Christine Mateus, Emilie Routier, Andrea Varga, David Malka, Alexandra Leary, Judith Michels, Jean-Marie Michot, Aurélien Marabelle, Olivier Lambotte, Zahir Amoura, Jean-Charles Soria, Sihem Kaaki, Nathalie Quellard, Jean-Michel Goujon and Isabelle Brocheriou

1Department of Nephrology, Peupliers Private Hospital, Ramsay Générale de Santé, Paris, France, 2UPEC (Université Paris Est Créteil), INSERM U955, Institut Mondor de Recherche Biomédicale (IMRB), Equipe, Créteil, France, 3Department of Internal Medicine, Pitie-Salpetriere Hospital, Paris, France, 4Drug Development Department (DITEP), Gustave Roussy, Villejuif, France, 5Department of Pathology, Pitie-Salpetriere Hospital, Paris, France, 6Department of Supportive Care, Gustave Roussy, Villejuif, France, 7Department of Medical Oncology, Dermatology Unit, Gustave Roussy, Villejuif, France, 8Department of Medical Oncology, Gastrointestinal Cancer Group, Gustave Roussy, Villejuif, France, 9Department of Medical Oncology, Gynecology Unit, Gustave Roussy, Villejuif, France, 10Department of Internal Medicine and Clinical Immunology, Bicêtre University Hospital, Le Kremlin Bicêtre, France and 11Department of Pathology, Electron Microscopy Unit, CHU Poitiers, Poitiers, France

Correspondence and offprint requests to: Hassan Izzedine; E-mail: h.izzedine@ramsaygds.fr

ABSTRACT

Objective. Expanded clinical experience with patients treated by pembrolizumab has accumulated. However, renal toxicities associated with this anti-programmed cell death 1 agent are poorly described because kidney histology is rarely sought. As a nephrology referral centre, we aimed to describe the clinic-biological and histopathological characteristics of pembrolizumab-related nephropathy and its response to treatment.

Methods. We conducted a monocentric large case series study, including all pembrolizumab-treated cancer patients presenting a renal toxicity addressed to our centre from 2015 to 2017.

Results. A total of 12 patients (7 men) out of 676 pembrolizumab-treated patients (incidence 1.77%) were included (median age 69.75 years). Patients were referred for acute kidney injury (n = 10) and/or proteinuria (n = 2). A kidney biopsy was performed in all patients, with a median duration of use of 9 months (range 1–24 months) after the beginning of treatment. Biopsy showed that four patients had acute interstitial nephritis (AIN), whereas five had acute tubular injury (ATI) alone, one had minimal change disease (MCD) and ATI, and one had MCD alone. Pembrolizumab withdrawal coupled with corticosteroid therapy was the most effective treatment for kidney function recovery. Drug reintroduction resulted in a more severe recurrence of AIN in one patient who required maintenance of pembrolizumab. Two patients died of cancer progression with one of them developing severe renal failure requiring dialysis.
Likewise, the safety profile of ICPIs has generated considerable efficacy in the management of a variety of cancers [2–4]. Extensive research was conducted over the past few years evaluating their potential as anti-cancer agents. Extensive restraint was used in the past few years evaluating their efficacy in the management of a variety of cancers [2–4]. Likewise, the safety profile of ICPIs has generated considerable research interest [5–9].

Pembrolizumab (KEYTRUDA®, Merck & Co., Inc., Kenilworth, NJ, USA) is a highly selective monoclonal IgG4-kappa (immunoglobulin G4-Kappa) isotype antibody that selectively binds to PD-1 blocking the receptor’s negative impact on lymphocyte function [10]. Pembrolizumab has been explored in a series of trials in patients with advanced melanoma and in other cancers such as renal cell carcinoma (RCC), lymphoma and others. In a pooled analysis based on randomized controlled trials including 3953 patients, the overall incidence of any pembrolizumab-based therapies emergent adverse events was 74.3% [95% confidence interval (CI): 0.671–0.805] [11] including all-grade rash (14.8%, 95% CI: 0.102–0.204), pain (13.7%, 95% CI: 0.011–0.689), pruritus (17.7%, 95% CI: 0.128–0.240), vitiligo (11.0%, 95% CI: 0.089–0.169), arthralgia (11.3%, 95% CI: 0.082–0.154) and dry mouth (10.0%, 95% CI: 0.045–0.206) [11]. There is, however, no mention of kidney disorders.

In this study, we conducted a prospective analysis of 12 biopsy-proven pembrolizumab-related nephropathies. We describe here the clinical and biological presentation of pembrolizumab-associated kidney disease, the kidney pathology data and the response to treatment.

**MATERIALS AND METHODS**

**Patients**

This is a single-centre large case series study concerning an observational cohort of patients. We analysed patients who were referred for acute kidney failure and/or proteinuria following pembrolizumab therapy and all of them underwent kidney biopsy (KB).

All patients gave informed consent for the anonymous use of their personal health data. Each patient medical record was thoroughly reviewed with the collection of clinical, biological and pathologic data at onset, at diagnosis, and at last follow-up. This study was approved by the local ethics committee and was in accordance with the Helsinki Declaration of 1975.

The clinical and laboratory studies were assessed at the time of KB, and follow-up data were available for all patients (Table 1). Each patient was followed over time for the development of specific endpoints, including progression to severe kidney failure and death.

**Histology**

All biopsy specimens had a part for light microscopy (fixed and prepared using standard techniques) and a part for immunofluorescence-labelling studies [immunoglobulin (Ig) G, IgM, IgA, Kappa and Lambda Ig light chains, fibrin, C3 and C1q anti-sera tests on frozen biopsies]. Kidney light microscopy specimens and immunofluorescence results were systematically reviewed by a senior pathologist without access to the patients’ files.

**Statistical analyses**

A two-sided chi-square test was used to compare all qualitative variables. Mann–Whitney rank testing was applied for all comparisons of quantitative variables. The results are expressed as mean values unless otherwise stated. A P < 0.05 was considered to be statistically significant.

**RESULTS**

**Clinicopathologic characteristics**

Twelve Caucasian patients (seven men) out of 676 pembrolizumab-treated patients in our centre were included in the study (incidence 1.77%). Median age was 69.75 years (range 46–84 years). The most common cancer was metastatic melanoma (nine patients, 75%). Other affected organs/cancers were Hodgkin’s lymphoma, endometrium and ileal neuroendocrine tumour (NET). Pembrolizumab was used at standard dosage (2 mg/kg intravenously every 3 weeks).

Kidney involvement occurred at a median time of 9 months (range 1–24 months) after the beginning of treatment, characterized by acute renal failure defined by an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² (11 patients, 91.5%), proteinuria (2 patients, 16.6%, with proteinuria > 3 g/day), microscopic haematuria (3 patients, 25%) and/or aseptic leukocyturia (4 patients, 33.3%). Mean serum creatinine (Scr) and aMDRD creatinine clearance were 96.4 µmol/L (range 70–147) and 62.5 mL/min/1.73 m² (range 43–80), respectively.

Kidney biopsies identified three distinct types of renal damage associated with pembrolizumab therapy: acute interstitial nephritis (AIN; four patients, 30%), acute tubular injury (ATI; five patients, 41.6%) and minimal change disease (MCD; two patients, 16.6%) (Figure 1). Patients with AIN also had tubulitis (four patients), flattening of the tubular epithelium (four patients) and interstitial fibrosis. No significant glomerular deposit was found by immunofluorescence analysis. Transmission electron microscopy analysis in nephrotic syndrome (NS) case (Patient 2) showed marked effacement of visceral epithelial cell foot processes in some areas (Figure 2). Histopathological findings are summarized in Table 2.

**Clinical outcome**

The median follow-up was 13 months (range 1–36 months).
Ten out of the 12 patients stopped pembrolizumab treatment. Of these 10 patients, 7 received steroids on top of pembrolizumab withdrawal and 1 patient was dialysed for 1 month and died because of melanoma evolution. The other six have a favourable renal evolution with a recovery of ~50% (mean GFR 27.3 versus 44.5 mL/min/1.73 m²) of their renal function (Table 3). For one patient, the reintroduction of pembrolizumab resulted in a more severe recurrence of AIN. Three of them are in complete remission, two patients remained tumour-active and one other patient died after 24 months due to the evolution of his illness. For the remaining three patients who did not receive corticosteroids, renal function remained stable (mean GFR 43.3 versus 42.6 mL/min/1.73 m²) and one patient remained in complete remission.

Two tumour-active patients maintained pembrolizumab treatment with a variable improvement of their kidney function (patient on corticosteroids, GFR 26 versus 40 mL/min/1.73 m², patient without corticosteroids GFR 43 versus 48 mL/min/1.73 m²).

**DISCUSSION**

This study, which is the largest series of biopsy-proven pembrolizumab-related nephropathies published so far, focused on the clinical, biological and pathological presentation of this complication. Kidney involvement related to pembrolizumab can lead to acute kidney injury (AKI) and/or NS associated with AIN, ATI and podocytopathy like MCD, respectively.

As previously reported, two different types of immune-related kidney injury have been reported under immune checkpoint inhibitors (ICPI) therapy: AIN and more rarely glomerular diseases [12, 13] (Table 4). Indeed, most of the ICPI-related AKI presented as acute tubulointerstitial nephritis (ATIN) pattern on kidney biopsies (88%), 25% of which were associated with granulomatous features [12–15]. The knowledge of the timing of

---

**Table 1. Characteristics of patients with biopsy-proven pembrolizumab-related renal involvement**

| Characteristic                                    | Value          |
|--------------------------------------------------|----------------|
| Number of patients                               | 12 patients    |
| Demography                                       | 7 M/5 F        |
| Age, years, median (IQR)                         | 69.75 (46–84)  |
| Comorbidities                                    |                |
| HT                                               | 5              |
| Diabetes                                         | 1              |
| MGUS IgG                                         | 1              |
| Horton disease                                   | 1              |
| Cancer type                                      |                |
| Metastatic melanoma                              | 9              |
| Hodgkin lymphoma                                 | 1              |
| Endometrial carcinoma                            | 1              |
| Ileal NET                                        | 1              |
| Previous anti-cancer drugs                       |                |
| Cisplatin/VP16                                   | 1              |
| Carboplatin/taxol                                | 1              |
| Ipilimumab                                       | 1              |
| Dabrafenib/trametinib                            | 1              |
| Renal involvement at presentation                |                |
| Time to KB, months (IQR)                         | 9 (1–24)       |
| Renal abnormalities                              |                |
| AKI                                              | 11             |
| NS                                               | 2              |
| Proteinuria                                      | 1              |
| Microscopic haematuria                           | 3              |
| Aseptic leucocyturia                             | 4              |
| Histological characteristics                     |                |
| AIN                                              | 6              |
| Plasma cell infiltration                         | 6              |
| + Tubulitis/ATI                                  | 6              |
| + Interstitial fibrosis, % (IQR)                 | 18.75 (0–50)   |
| ATI                                              | 4              |
| MCD                                              | 2              |
| Crystal                                          | 1              |
| Superimposed NAS                                 | 10             |

IQR: interquartile range; F, female; HT, hypertension; M, male; MGUS: monoclonal gammopathy of undetermined significance; NAS: nephroangiosclerosis.

---

**FIGURE 1: Pathological findings in pembrolizumab-related nephropathies (Masson’s trichrome).** (A) Nephron segments with flattened tubular epithelium and loss of brush border defining ATI. (B) AIN with interstitial oedema and lymphoplasmacytic infiltrate associated with tubulitis. (C) Preserved cortical area with normal-appearing glomerulus in this patient with NS.

**FIGURE 2:** Diffuse foot process effacement (magnification ×6000)
onset of AKI may not be as helpful as in other immune-related adverse events (irAE). However, extrarenal irAE such as hypophysitis and colitis preceded AKI in half of the cases, the existence of which might have helped diagnose renal irAE.

ATI

About half of our patients had ATI. Those patients had more frequently cardiovascular risk factors and marked histological vascular lesions and are more frequently men than AIN patients. Two of them received platinum but at least 1 year before pembrolizumab was introduced. None of our patients was treated with non-steroidal anti-inflammatory drugs or BRAF (B-Raf proto-oncogene) inhibitors. Thus, the underlying vascular field may have favoured the occurrence of ATI without being the cause. In fact, decrease in kidney function occurred after pembrolizumab started. We believe that the ATI is due to pembrolizumab related to an unknown mechanism (Table 5).

This is an important point as many oncologists presume that AKI developing with ICPI therapy is due to AIN and treat with steroids without getting a biopsy. This would be the incorrect therapy for AKI in such patients. Hence, there is a requirement for more such studies of KB tissue to work out the pathomechanism of kidney injury by these drugs.
in some cases, extending beyond drug cessation (2 months) and the development of kidney injury [14, 18–20].

Although initial studies showed a low incidence of AKI associated with ICPI, emerging data suggest an incidence ranging from 9.9% to 29.0% [21].

The mechanism of injury is assumed to involve cell-mediated immunity as other drug-induced AIN as T-cell-dominant infiltration of the kidney interstitium. ICPI therapy may promote a permissive environment for the migration of T-cell effector(s) into the kidneys, thus initiating an inflammatory response that could clinically lead to ATIN [22]. ICPIs 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. It is noteworthy that 14 out of the 19 patients reported by Cortazar et al. [15] and Shirali et al. [14] were on culprit drugs associated with ATIN (proton pump inhibitors and non-steroidal anti-inflammatory drugs) [23]. Thereby, KB is needed as patients frequently have ATI/ATN, which is likely unrelated to the ICPI. This will allow the clinician to potentially continue the ICPI without exposing the patient to corticosteroids. Alternatively, ICPIs could synergistically potentiate antigen recognition and T-cell proliferation in lymph nodes and provoke untethered cytotoxic T-cell effects in the periphery, not only against the tumour, but also against normal tissues [20].

### Glomerulonephritis

To our knowledge, only a few other cases of glomerulopathies, mainly podocytopathy-like minimal change nephropathy/focal segmental glomerulosclerosis (MCN/FSGS) (n = 7), immune complex glomerulonephritis (GN) (n = 3) or proteinase 3 anti-neutrophil cytoplasmic auto-antibodies (PR3-ANCA) vasculitis (n = 1) associated with cancer immunotherapy, have been described [24–31] (Table 6).

As shown in Table 5, glomerular disease occurred after 1–72 weeks of therapy with ipilimumab (three cases), nivolumab (three cases) and pembrolizumab (five cases including ours). These cases highlight the variable and often prolonged time course between drug exposure (1 week to 18 months) and clinical recognition of kidney injury. In these cases, ICPI therapy was prescribed for various cancers [metastatic melanoma (five), renal cell carcinoma (two), Hodgkin’s lymphoma, lung squamous cell carcinoma (LSCC), mesothelioma and ileal NET (one each)]. In 10 patients, kidney histology was obtained with a diagnosis of podocytopathy-like MCD/FSGS (two, one and four cases for ipilimumab, nivolumab and pembrolizumab, respectively), lupus-like membranous nephropathy (MN) (ipilimumab, one case) or IgA nephropathy (nivolumab, two cases). One patient on ipilimumab had additional inflammatory interstitial infiltrate (associated with MCN) and three patients on pembrolizumab or nivolumab, ATI. One patient developed rapid glomerulatosis with poyangiitis and vasculitis unleashed by pembrolizumab treatment. Oral cyclophosphamide (CYC), 150 mg once daily and pulse methyl prednisone induced rapid resolution of symptoms [31].

Treatment with glucocorticoids coupled with discontinuation of ICPIs resulted in complete improvement of proteinuria and/or kidney function. One patient (pembrolizumab) required transient haemodialysis and died because of melanoma evolution. Two patients (pembrolizumab and nivolumab, one patient each) required transient haemodialysis. In one case of MCD with ipilimumab, complete remission of NS was observed under drug withdrawal with steroid use. Two years later, ipilimumab was restarted as salvage therapy. Four months following reintroduction of ipilimumab therapy, the patient developed

### Table 5. Clinical characteristics of patients under pembrolizumab (ATI versus AIN)

|                     | ATI (n = 5) | AIN (n = 4) |
|---------------------|------------|------------|
| Age, years          | 59–84      | 62–86      |
| Gender              | 3 M        | 3 F        |
| SBP, mmHg           | 125–150    | 150        |
| DBP, mmHg           | 70–90      | 70–80      |
| Underlying AKI risk factors | T2DM (1)   | T2DM (1)   |
|                     | IHD (1)    | MGUS (1)   |
|                     | Carcinoid HD (1) | Horton disease (1) |
|                     | Stroke (1) | ARA (1)    |
|                     | ARA (4) and Diuretic (3) |              |
| Previous chemotherapy | Platin (2), Dabrafenib, trametinib (3) |              |
| Cancer              | Melanoma (3) | Melanoma (4) |
|                     | Ileal NET (1) | Endometrial (1) |
| Vascular changes on KB | Discrete to moderate | Normal to discrete |

SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hypertension; T2DM, type 2 diabetes mellitus; IHD, ischaemic heart disease; ARA, angiotensin receptor antagonist; M, male; F, female; MGUS, monoclonal gammopathy of undetermined significance.
Table 6. Clinicopathological features of cancer patients with glomerular diseases associated with ICPIs use

| Drug [Ref] | Cancer type | Prior therapy and potential nephrotoxins | Timing of glomerular disorders | Renal findings and kidney function | Kidney pathological findings | Clinical course |
|------------|-------------|-------------------------------------------|-------------------------------|-----------------------------------|-----------------------------|-----------------|
| Ipilimumab [24] | Melanoma | conventional chemotherapy | 6 weeks | NS: SAlb 2.45 g/dL, Pu 7.5 g/day | Lupus-like MN | 12 months after diagnosis, only non-nephrotic proteinuria (1 g per day) persisted after discontinuation of ipilimumab therapy and a short course of steroid |
| Ipilimumab [26] | Melanoma | TMZ, sorafenib | 18 months | NS: SAlb 2.6 g/dL, Pu 9.5 g/day | MCD | Proteinuria largely remitted (0.39 g/day) following discontinuation of ipilimumab and treatment with corticosteroids (prednisone, 1 mg/kg) initiated and tapered over 4 months |
| Ipilimumab restarted | | | 4 months | Recurrence of NS | | Ipilimumab therapy was again discontinued, with subsequent remission of proteinuria |
| Ipilimumab [25] | Melanoma | not reported | 2 weeks | NS: SAlb 2.2 g/dL, Pu 9 g/day | MCD and AIN | Renal function improved and NS resolved under high-dose steroids |
| Nivolumab [27] | Papillary RCC | not reported | 8 weeks | NS: SAlb 1.9 g/dL, Pu 17 g/day | FSGS | High-dose corticosteroids + mycophenolate mofetil resulted in remission of the NS and recovery of renal function. Proteinuria subsequently relapsed during corticosteroid tapering |
| Nivolumab [28] | LSCC | not reported | 6 months | Pu 3 g/day and microhaematuria | IgA nephropathy | Improvement of proteinuria (0.24 g/day) and AKI (SCr, 132 μmol/L) 4 months following cessation of nivolumab therapy |
| Nivolumab [29] | RCC | pazopanib | 10 months | Pu 3 g/day and microhaematuria | Crescentic IgA nephropathy + ATI | After 5 months of cessation of nivolumab, high dose of steroids and haemodialysis, the patient’s kidney function improved to his baseline level (159 μmol/L) |
| Pembrolizumab [26] | Hodgkin lymphoma | not reported | 4 weeks | NS: SAlb 1.8 g/dL, Pu 10.3 g/day | MCD and ATI | Improvement of proteinuria (3.1 g/day) and AKI (SCr, 132 μmol/L) 6 months following cessation of pembrolizumab therapy with tapering corticosteroid treatment |
| Pembrolizumab [30] | Mesothelioma | CPV | 8 weeks | NS: SAlb 1.5 g/dL, Pu 19 g/day | MCD | Creatinine values normalized and proteinuria resolved within 5 days following cessation of pembrolizumab with initiation of prednisone and angiotensin II receptor blocker |
| Pembrolizumab [31] | Melanoma | ipilimumab, dacarbazine | 1 week | Proteinuria, haematuria | KB not performed | Diagnosis of granulomatosis with polyangiitis after sequential immune checkpoint inhibition with ipilimumab and pembrolizumab and improvement after 3 weeks of high-dose steroids and cyclophosphamide (CYF) |
| Pembrolizumab, our case | Melanoma | not reported | 4 weeks | NS: SAlb 1.7 g/dL, Pu 6 g/day | MCD and ATI | Improvement of proteinuria under steroid treatment. However, patient was dialysed for 1 month and died because of melanoma evolution |
| Pembrolizumab, our case | Ileal NET | cisplatin, VP16 | 18 months | SAlb 4.2 g/dL, Pu 3.5 g/day | MCD | No change on renal parameters under maintenance of pembrolizumab without steroids |

Cpt, complement; CPV, carboplatin pemetrexed vinorelbine; Pu, proteinuria; SAlb, serum albumin level; TMZ, temozolomide.
recurrence of proteinuria and NS. Ipilimumab therapy was again discontinued, with subsequent remission of proteinuria [26]. The remaining patient (our second patient) with NS who did not receive corticosteroids while maintaining pembrolizumab, had no improvement in kidney parameters.

We distinguish two glomerular disease type: podocytopathy-like MCD/FSG and immune complex GN.

(i) Among the podocytopathy-like MCD/FSG, cancers and in particular haemopathies (Hodgkin’s lymphoma) and drugs are the most common causes [32–37].

Besides the proposed mechanism based on a remote production of a ‘permeability factor’ that may cause release of cytokines promoting podocyte foot-process effacement via candidate factors such as vascular endothelial growth factor, which is known to act on systemic capillaries and the glomerular permeability barrier [38, 39], the pathogenesis of NS/MCD can be explained otherwise. Indeed, the finding of de novo podocyte CD80 expression in NS may suggest a more direct link between the innate immune response and podocyte injury [26, 40]. Interestingly, both the PD-1 and CTLA-4 pathways modulate T-cell activation through signals involving antigen-presenting cell CD80 (B7-1) [41, 42]. As such, a direct effect by these agents on podocyte CD80 (B7-1) may also be possible [26]. However, there remains a doubt about the MCD mechanism (cancer or drug-related) since PD-1 was not performed on the kidney biopsies.

(ii) Three immune complex GN cases are reported [lupus-like MN (n = 1) and IgA nephropathy with (n = 1) or without (n = 1) crescentic GN].

PD-1 checkpoint knockout mice developed glomerulonephritis [43] suggesting that PD-1 signalling pathway is important for minimizing T-cell-mediated renal inflammation. Although it may be difficult to prove a causal relationship between IgA nephropathy and ICPI therapy, recent studies have shown that galactose-deficient IgA molecules and anti-glycan antibodies play a role in immune complex formation in patients with IgA nephropathy [44], suggesting a possible role of nivolumab in the occurrence of IgA nephropathy cases [27–29]. However, there might be some association as IgA nephropathy is very common in the world and it is not certain whether ICI is triggering anything there.

(iii) Additionally, one case of positive PR3-ANCA granulomatosis polyangiitis (GPA) related to pembrolizumab treatment has been reported. Unfortunately, KB was not performed despite proteinuria and haematuria. Likewise, several forms of vasculitis, including large-vessel vasculitis have been reported after ipilimumab treatment [24, 45, 46]. Together, aberrant expression of PD-1 on Th cells in GPA [47] and polymorphisms in PDCD1 (the gene encoding PD-1) and the cytotoxic T-lymphocyte-associated protein 4 (CLTA4) gene [48] are reported to play a role in the pathophysiology of GPA, highlighting the important role of PD-1 in the development of GPA [31].

Such pathophysiological hypotheses merit further investigation to improve our understanding of the immunopathogenesis of these poorly understood glomerular diseases [26].

CONCLUSION

Given the increasing prevalence of ICPI therapies, the small incidence of kidney adverse events and the fact that glomerular disorders are atypical, physicians need to pay more attention to the possible renal side effects. Early biopsy and use of corticosteroids may be warranted in some cases.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Johnson DB, Sullivan RJ, Menzies AM. Immune checkpoint inhibitors in challenging populations. Cancer 2017; 123: 1904–1911
2. Lynch T, Bondarenko I, Luft A et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter Phase II study. J Clin Oncol 2012; 30: 2046–2054
3. Kwon ED, Drake CG, Scher HI et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (ca184–043): a multicentre, randomised, double-blind, Phase 3 trial. Lancet Oncol 2014; 15: 700–712
4. Eggermont AM, Chiarion-Silieri V, Grob JJ et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. N Engl J Med 2016; 375: 1845–1855
5. Horinouchi H, Yamamoto N, Fujiwara Y et al. Phase I study of ipilimumab in phased combination with paclitaxel and carboplatin in Japanese patients with non-small-cell lung cancer. Invest New Drugs 2015; 33: 881–889
6. Margolin K, Ernstoff MS, Hamid O et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, Phase 2 trial. Lancet Oncol 2012; 13: 459–465
7. Aglietta M, Barone C, Sawyer MB et al. A Phase I dose escalation trial of tremelimumab (cp-675, 206) in combination with gemcitabine in chemotherapy-naive patients with metastatic pancreatic cancer. Ann Oncol 2014; 25: 1750–1755
8. Mcdermott DF, Drake CG, Szol M et al. Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab. J Clin Oncol 2015; 33: 2013–2020
9. Mcneel DG, Smith HA, Ekichof JC et al. Phase I trial of tremelimumab in combination with short-term androgen deprivation in patients with PSA-recurrent prostate cancer. Cancer Immunol Immunother 2012; 61: 1137–1147
10. Hamid O, Robert C, Daud A et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med 2013; 369: 139–144
11. Wang M, Ma X, Guo L et al. Safety and efficacy profile of pembrolizumab in solid cancer: pooled reanalysis based on randomized controlled trials. Drug Des Devel Ther 2017; 11: 2851–2860
12. Izzedine H, Mateus C, Boutros C et al. Renal effects of immune checkpoint inhibitors. Nephrol Dial Transplant 2017; 32: 936–942
13. Jhaiver KD, Perazella MA. Adverse events associated with immune checkpoint blockade. N Engl J Med 2018; 378: 1163
14. Shirali AC, Perazella MA, Gettinger S. Association of acute interstitial nephritis with programmed cell death 1 inhibitor therapy in lung cancer patients. Am J Kidney Dis 2016; 68: 287–291
15. Cortazar FB, Marrone KA, Troxell ML et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. Kidney Int 2016; 90: 638–647
16. Harmankaya K, Erasim C, Koellblinger C et al. Continuous systemic corticosteroids do not affect the ongoing regression of metastatic melanoma for more than two years following ipilimumab therapy. Med Oncol 2011; 28: 1140–1144
17. Bavi P, Kiehl R, Adeyi O. Immune-related adverse events (irAEs) following CTLA-4 and PD-1/PD-1 blockade in...
advanced melanoma: a comprehensive rapid autopsy study. Mod Pathol 2016; 29 (Suppl 2): 4A
18. Eigentler TK, Hassel JC, Berking C et al. Diagnosis, monitoring and management of immune-related adverse drug reactions of anti-PD-1 antibody therapy. Cancer Treat Rev 2016; 45: 7–18
19. Izzedine H, Gueutin V, Gharbi C et al. Kidney injuries related to ipilimumab. Invert New Drugs 2014; 32: 769–773
20. Murakami N, Borges TJ, Yamashita M et al. Severe acute interstitial nephritis after combination immune-checkpoint inhibitor therapy for metastatic melanoma. Clin Kidney J 2016; 9: 411–417
21. Wanchoo R, Karam S, Uppal NN et al. Adverse renal effects of immune checkpoint inhibitors: a narrative review. Am J Nephrol 2017; 45: 160–169
22. Perazella MA. Checkmate: kidney injury associated with targeted cancer immunotherapy. Kidney Int 2016; 90: 474–476
23. Troxell ML, Higgins JP, Kambham N. Antineoplastic treatment and renal injury: an update on renal pathology due to cytotoxic and targeted therapies. Adv Anat Pathol 2016; 23: 310–329
24. Fadel F, El Karoui K, Knebelmann B. Anti-CTLA4 antibody induced lupus nephritis. N Engl J Med 2009; 361: 211–212
25. Kidd JM, Gizaw AB. Ipilimumab-associated minimal change disease. Kidney Int 2016; 89: 720
26. Kitchlu A, Fingrut W, Avila-Casado C et al. Nephrotic syndrome with cancer immunotherapies: a report of 2 cases. Am J Kidney Dis 2017; 70: 581–585
27. Daanen RA, Maas RJH, Koornstra RHT et al. Nivolumab-associated nephrotic syndrome in a patient with renal cell carcinoma: a case report. J Immunother 2017; 40: 345–348
28. Kishi S, Minato M, Saijo A et al. Kidney Int 2016; 90: 474–476
29. Jung K, Zeng X, Bilusic M. Nivolumab-associated acute minimal change disease. Kidney Dis 2017; 9: 303–308
30. Alpers CE, Cotran RS. Neoplasia and glomerular injury. Kidney Int 1986; 30: 465–473
31. van den Brom RRH, Wayel H, Abdulahad WH et al. Rapid granulomatosis with polyangiitis induced by immune checkpoint inhibition. Rheumatology 2016; 55: 1145–1147
32. Alpers CE, Cotran RS. Neoplasia and glomerular injury. Kidney Int 1986; 30: 465–473
33. Dabbs DJ, Striker LM, Mignon F et al. Glomerular lesions in lymphomas and leukemias. Am J Med 1986; 80: 63–70
34. Glassock RJ. Secondary minimal change disease. Nephrol Dial Transplant 2003; 18 (Suppl 6): v552–v558
35. Auguet T, Lorenzo A, Colomer E et al. Recovery of minimal change nephrotic syndrome and acute renal failure in a patient with renal cell carcinoma. Am J Nephrol 1998; 18: 439–435
36. Martinez-Vea A, Panisello JM, Garcia C et al. Minimal change glomerulopathy and carcinoma. Report of two cases and review of the literature. Am J Nephrol 1993; 13: 69–72
37. Izzedine H, Escudier B, Lhomme C et al. Kidney diseases associated with anti-vascular endothelial growth factor (VEGF): an 8-year observational study at a single center. Medicine (Baltimore) 2014; 93: 333–339
38. Lagraue G, Xheneumont S, Branellec A et al. A vascular permeability factor elaborated from lymphocytes. I. Demonstration in patients with nephrotic syndrome. Biomedicine 1975; 23: 37–40
39. McCarthy ET, Sharma M, Savin VJ. Circulating permeability factors in idiopathic nephrotic syndrome and focal segmental glomerulosclerosis. Clin J Am Soc Nephrol 2010; 5: 2115–2121
40. Reiser J, von Gersdorff G, Loos M et al. Induction of B7-1 in podocytes is associated with nephrotic syndrome. J Clin Invest 2004; 113: 1390–1397
41. Yu CC, Fornoni A, Weins A et al. Abatacept in B7-1-positive proteinuric kidney disease. N Engl J Med 2013; 369: 2416–2423
42. Gagliardini E, Novelli R, Corna D et al. B7-1 is not induced in podocytes of human and experimental diabetic nephropathy. J Am Soc Nephrol 2016; 27: 999–1005
43. Nishimura H, Nose M, Hiai H et al. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. Immunity 1999; 11: 141–151
44. Suzuki H, Kiylyuk K, Novak J et al. The pathophysiology of IgA nephropathy. J Am Soc Nephrol 2011; 22: 1795–1803
45. Goldstein BL, Gedmintas L, Todd DJ. Drug-associated myalgia rheumatica/giant cell arteritis occurring in two patients after treatment with ipilimumab, an antagonist of CTLA-4. Arthritis Rheumatol 2014; 66: 768–769
46. Minor DR, Bunker SR, Doyle J. Lymphocytic vasculitis of the ureter in a patient with melanoma receiving ipilimumab. J Clin Oncol 2013; 13: e356
47. Wilde B, Hua F, Dolf S et al. Aberrant expression of the negative costimulator PD-1 on T cells in granulomatosis with polyangiitis. Rheumatology 2012; 51: 1188–1197
48. Slot MC, Sokolowska MG, Savelkous KG et al. Immunoregulatory gene polymorphisms are associated with ANCA-related vasculitis. Clin Immunol 2008; 128: 39–45