Long-term control by immune checkpoint inhibitors in a lung cancer patient with chronic kidney disease

Dlouhodobá léčba checkpoint inhibitory u pacienta s karcinomem plic a chronickým onemocněním ledvin

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Summary

Background: Immune checkpoint inhibitor (ICI) therapy has brought about a revolutionary advance in the treatment of advanced non-small cell lung cancer (NSCLC). Not a few patients with NSCLC have comorbid diseases. In patients who already have impaired renal function, particular attention must be paid to renal toxicity, a rare immune-related adverse events. Although there have been some case reports of ICI therapy for patients with advanced NSCLC undergoing hemodialysis, information on ICI therapy in patients with chronic kidney disease (CKD) is limited. ***Case:*** We show herein a case with a successfully treated 75-year-old male patient with CKD and advanced NSCLC. His estimated glomerular filtration rate at the start of anticancer treatment was 40 mL/min/1.73 m^2. Nivolumab and ipilimumab were administered, considering both the expectation of therapeutic efficacy and the avoidance of side effects. Ipilimumab was discontinued 1 year after the start of the treatment, and nivolumab was also terminated 2 years after the initiation of the treatment due to thyroid dysfunction as immune-related adverse event. Without worsening of CKD, the patient was able to control NSCLC with two immune checkpoint inhibitors for ≥ 3 years. ***Conclusion:*** Nivolumab and ipilimumab regimen might become one of the options for NSCLC patients with CKD. This report could provide some suggestions for the treatment of future patients who might experience a similar course of the therapy.

Key words

immune checkpoint inhibitor – chronic kidney disease – lung cancer – squamous cell carcinoma

Souhrn

Východiska: Léčba checkpoint inhibitory (immune checkpoint inhibitor – ICI) přinesla v léčbě pokročilého nemalobuněčného karcinomu plic (non-small cell lung cancer – NSCLC) revoluční pokrok. Nemálo pacientů s NSCLC má komorbidní onemocnění. U pacientů, kteří již mají poškozenou funkci ledvin, je třeba věnovat zvláštní pozornost renální toxicitě, což je vzácná imunitně podmíněná nežádoucí příhoda. Ačkoli bylo publikováno několik kazuistik léčby ICI u pacientů s pokročilým NSCLC podstupujících hemodialýzu, informace o léčbě ICI u pacientů s chronickým onemocněním ledvin (chronic kidney disease – CKD) jsou limitované. ***Případ:*** Uvádíme zde případ úspěšně léčeného 75letého pacienta s CKD a pokročilým NSCLC. Odhadovaná rychlost glomerulární filtrace na začátku protinádorové léčby byla 40 ml/min/1,73 m^2. Byl podán nivolumab a ipilimumab, jednak s ohledem na očekávaný terapeutický účinek a jednak kvůli zamezení nežádoucím účinkům. Ipilimumab byl vysazen 1 rok po zahájení léčby a podávání nivolumabu bylo také ukončeno, a to 2 roky od zahájení léčby kvůli dysfunkci štítné žlázy jako imunitně podmíněnému nežádoucímu účinku. Bez toho, aby se u pacienta zhoršilo CKD, byla možná léčba NSCLC dvěma checkpoint inhibitory po dobu ≥ 3 let. ***Závěr:*** Režim nivolumab a ipilimumab se může stát jednou z možností léčby pacientů s NSCLC a současně s CKD. Tento článek by mohl poskytnout návrh léčby budoucích pacientů, u kterých je možné předpokládat podobný průběh.

Klíčová slova

checkpoint inhibitor – chronické onemocnění ledvin – karcinom plic – dlaždicobuněčný karcinom

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Introduction

Comorbidities have a significant impact on survival in advanced lung cancer. As with several other cancers, many of them are aged, and perhaps because of this, they have decreased renal function. Cytotoxic drugs containing platinum are still used to treat advanced lung cancer [1], therefore, special attention should be paid to renal damage as an adverse event when treating patients with decreased renal function. Patients who meet the criteria of kidney damage or glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 for ≥ 3 months, irrespective of its cause, are considered to have chronic kidney disease (CKD) [2,3]. Currently, there is no established standard antitumor treatment for patients who meet the definition of CKD. In recent years, immune checkpoint inhibitors (ICIs) have emerged as therapeutic agents for advanced non-small cell lung cancer (NSCLC) [4]. Among them, anti-programmed death-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies have been the two of the first ICIs to be put into clinical practice and have contributed to improving the long-term prognosis [4]. Combination therapy with these two ICIs has also been introduced [5]. In addition to improved survival in patients with preserved major organ function, successful ICI monotherapy has been reported in a small number of NSCLC patients undergoing hemodialysis [6–9]. Immune-related adverse events (irAEs) caused by ICI therapy can occur in organs and parts of the body, and renal toxicity is no exception [10]. The most common underlying pathology is acute tubulointerstitial nephritis and usually presents initially as an increase in the serum creatinine level without any clinical signs or symptoms. Electrolyte disturbances, oliguria, anuria, and swelling might develop [10]. However, there is very limited information regarding ICI treatment outcomes for advanced NSCLC patients with CKD [11–13].

We show herein a case of a 75-year-old NSCLC patient with CKD who was able to control NSCLC without worsening of CKD for ≥ 3 years with the combined therapy of anti-PD-1 and anti-CTLA-4. To our best knowledge, this is the first advanced NSCLC patient with CKD who could be controlled with the combination of two ICIs for a long time without worsening renal function.

Case report

A 75-year-old man was referred to our hospital due to chest abnormal opacity detected in mass screening. He had a history of smoking 40 packs per year but had no history of diabetes. His physical examination was unremarkable and performance status (Eastern Cooperative Oncology Group – ECOG) was 0. Laboratory tests revealed ele-

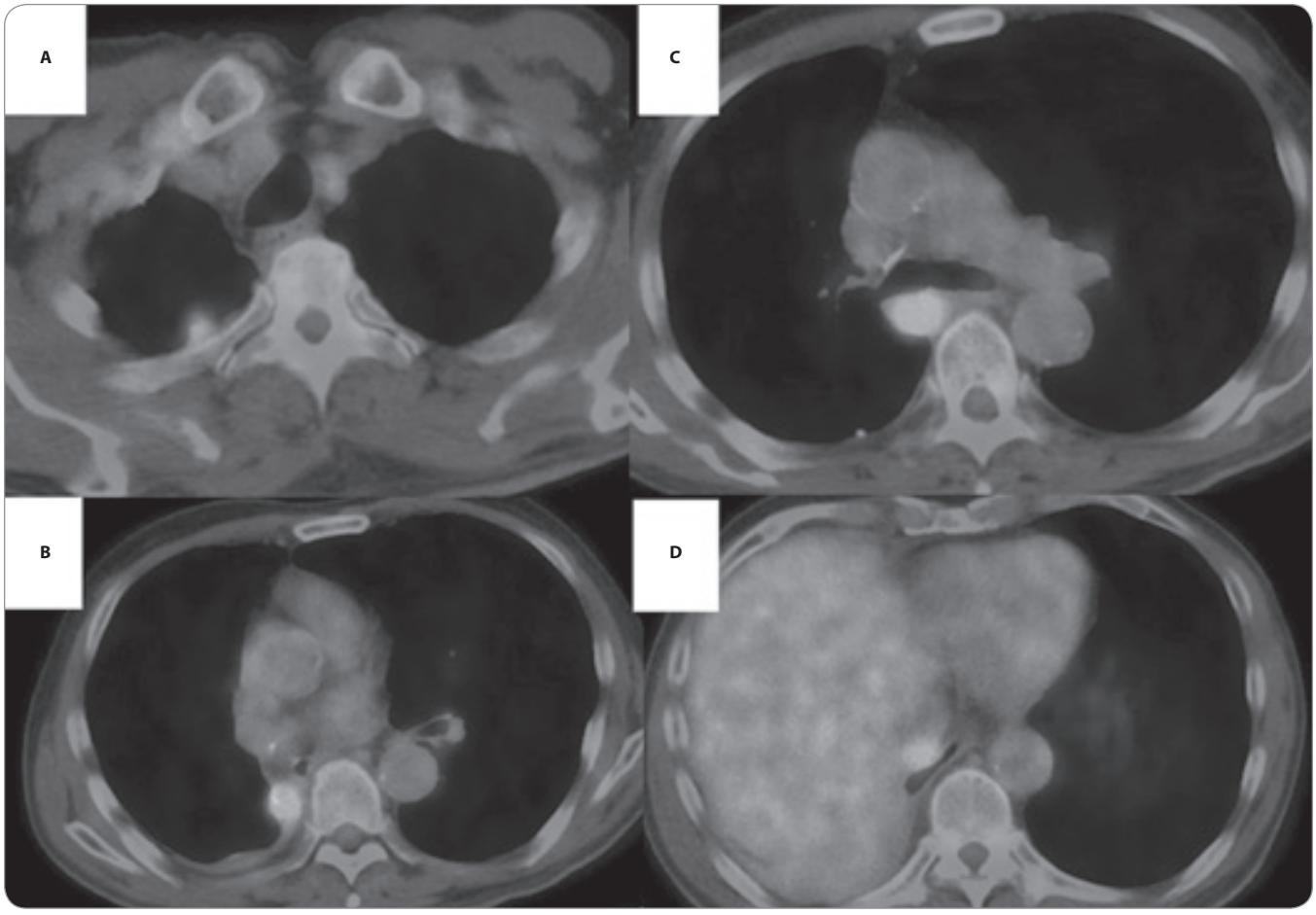

Fig. 1. PET/CT scan 6 months after surgery revealed pleural dissemination (A, B) and recurrence in mediastinal lymph nodes (C, D).

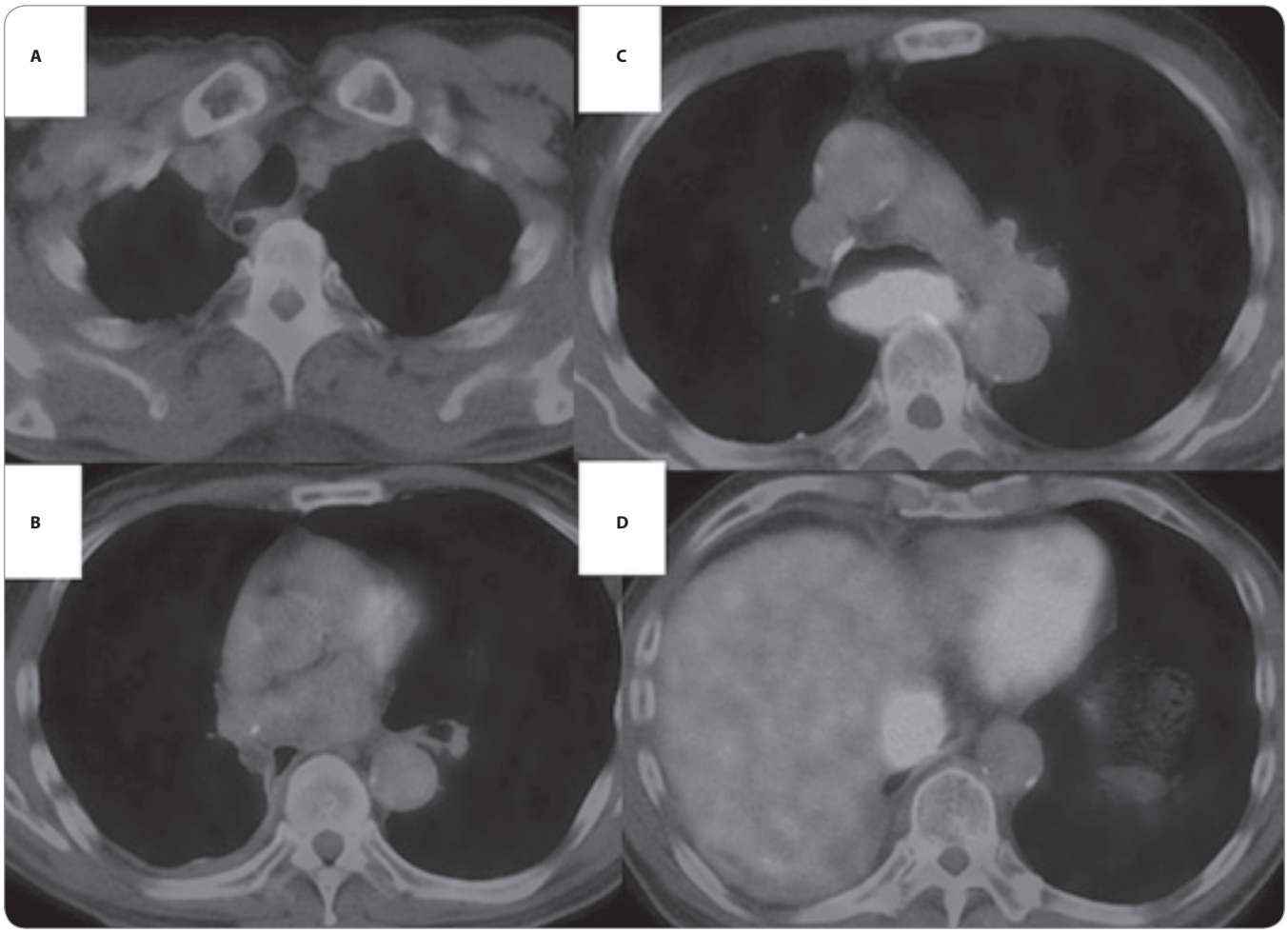

Fig. 2. PET/CT scan taken 18 months after the initiation of the therapy revealed disappearance of pleural dissemination (A, B) but deterioration of the reasons in the mediastinal lymph nodes (C, D).

vated serum creatinine (2.13 mg/dL, normal range < 1.04 mg/dL), blood urea nitrogen (BUN) (33.2 mg/dL, normal range < 22.0 mg/dL), and estimated glomerular filtration rate (e-GFR) (41.0 mL/min/1.73 m^2). We concluded that he had CKD. High blood pressure and aging were evaluated as the causes of CKD. A chest computed tomography (CT) scan revealed a 38 mm irregular tumor in the right lower lobe. Transbronchial lung biopsy from the lesion was performed, and the pathological diagnosis was squamous cell carcinoma. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) revealed no distant metastases. Magnetic resonance imaging of the head revealed no brain metastases. The clinical stage was IIB (cT2aN0M0). PD-L1 expression was assessed by immunohistochemistry assay (Dako, Carpinteria, CA) using mouse 22C3 anti-human PD-L1 antibody, and the tumor proportion score (TPS) was 80%. Right lower lung lobectomy and mediastinal lymph node dissection were performed, and the pathological diagnosis was IIB (cT2aN0M0). Postoperative adjuvant treatment was not performed because the patient did not wish to undergo it, and because both the patient and the medical staff wanted to avoid worsening of renal function due to adjuvant therapy containing platinum drugs. PET/CT scan 6 months after surgery revealed pleural dissemination (Fig. 1A, B) and recurrence in mediastinal lymph nodes (Fig. 1C, D). Treatment with nivolumab and ipilimumab (Checkmate 227 regimen) was selected in consideration of decreased renal function, expectations for therapeutic efficacy, and avoidance of side effects of cytotoxic anticancer drugs. PET/CT scan taken 18 months after the initiation of the therapy revealed disappearance of pleural dissemination (Fig. 2A, B) but deterioration of the lesions in mediastinal lymph nodes (Fig. 2C, D). As there was no other metastatic lesions, irradiation to these mediastinal lesions was performed. Immediately after completing this radiotherapy, only nivolumab was resumed considering the influence of radiation therapy. These lesions shrank with radiation, and CT performed 3 years after starting nivolumab and ipilimumab therapy showed no recurrence (Fig. 3A, B). The eGFR value has been continuously investigated, but no worsening has been observed to date (Fig. 4).

Discussion

The advent of ICIs has revolutionized the treatment of advanced NSCLC [4]. As for ICI treatment for NSCLC, it became pos-

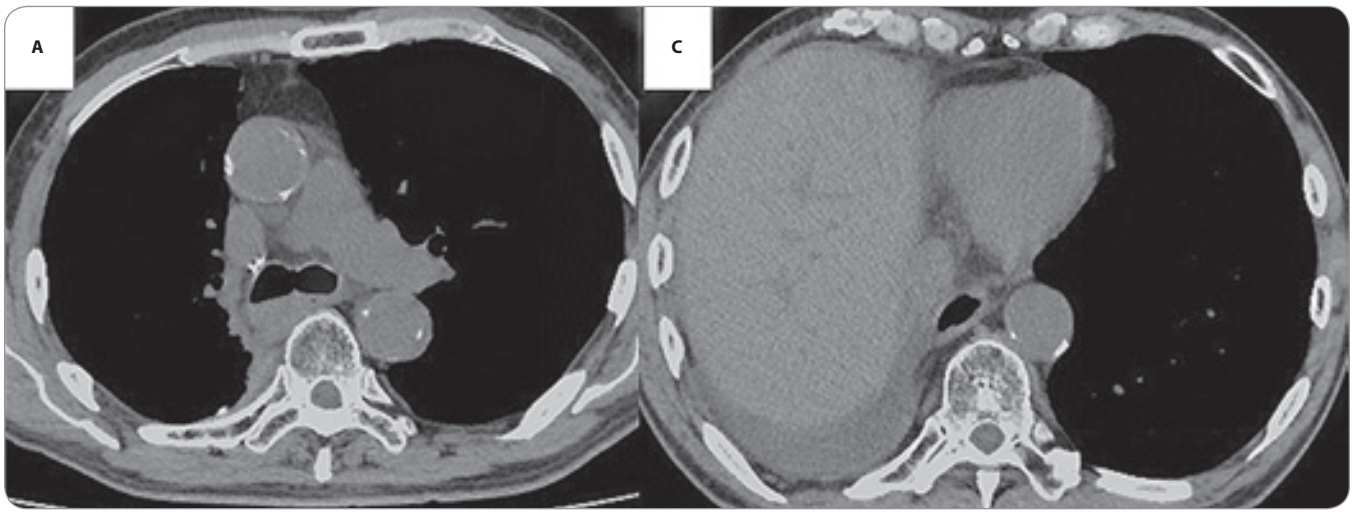

Fig. 3. Chest CT performed 2 years after starting nivolumab and ipilimumab therapy shows no recurrence (A, B).

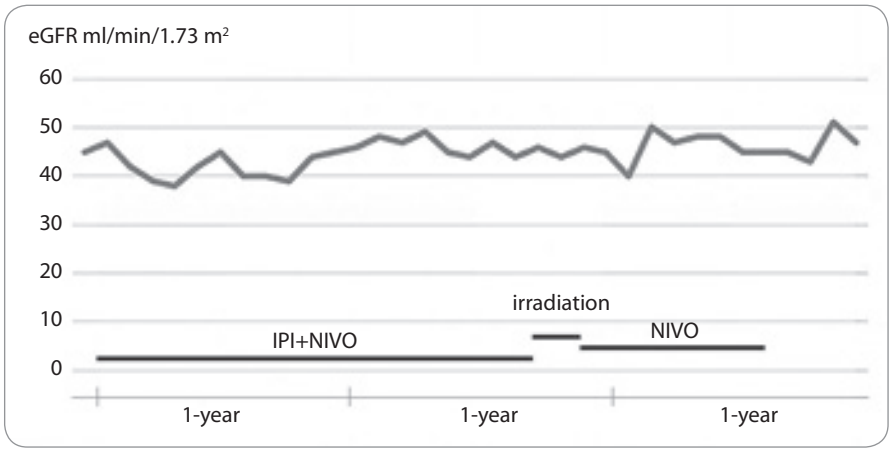

Fig. 4. Changes in eGFR values since the start of the treatment. No exacerbation of eGFR has been observed to date.
eGFR – estimated glomerular filtration rate, IPI – ipilimumab, NIVO – nivolumab

sible to administer ICI alone, and then in combination with cytotoxic drugs to improve response rates [4]. In addition to them, a combination therapy (Checkmate 227 regimen) [5] with two different types of ICIs has also come into clinical practice. The incidences of renal irAEs in these clinical trials, whether in ICI monotherapy, ICI combined with cytotoxic anticancer drugs, or even in combination of ICIs, were reported to be low [14,15]. Even though the results were obtained in clinical trials, these trials were only performed in patients with preserved major organ function, including renal function [14,15]. Therefore, for advanced NSCLC patients with CKD, evidence-based recommended anticancer treatment has not been established. In current clinical practice, renal irAEs have been most often manifested as acute kidney injury, with an incidence of 3–5% [16–20]. Manohar et al. recently reported the overall incidence of acute kidney injury (AKI) to be 4.2% in a meta-analysis of 48 clinical trials with a total of 11,482 patients [21]. A report by Sarah et al. showed that the incidence of AKI directly related to ICI was only 0.8%. There were many reports that the frequency of AKI was the same with PD-1 and CTLA-4 antibodies [22]. Cortazar et al. showed that the incidence of AKI with nivolumab and ipilimumab was 2% and 1.9%, respectively, and with their combination 4.9% [19]. Although some cases of successful ICI monotherapy have been reported [6–9], there were only three reports regarding ICI treatment of NSCLC patients with CKD [11–13]. The first was a study by Herz et al. [11]. In their four melanoma patients treated with antiPD-1 antibody monotherapy, none showed worsening of renal function during the treatment with monotherapy. The second was a study by Kanz et al. [12]. They investigated the efficacy and safety of anti-PD-1 antibody monotherapy in 17 patients with renal impairment (serum creatinine ≥ 2.0 mg/dL and e-GFR ≤ 30 mL/min/1.73 m^2) [12]. According to the authors, anti-PD-1 antibody therapy might be considered in patients with impaired renal function under appropriate clinical monitoring [12]. The third was a study by Epi et al. [13]. They investigated the renal adverse effects of ICI therapy in 364 patients. Thirteen patients developed AKI, all of whom received anti-PD-1 antibody monotherapy. Their study included four patients who received two different ICIs, ipilimumab and nivolumab, but none of them developed AKI. They also showed that the administration of ICIs in CKD patients, defined as eGFR < 60 mL/min, was not associated with a greater risk of ICI-induced AKI in univariate and multivariate analyses [13]. However, there is no description of their long-term prognosis in this study. To our best knowledge, this patient was therefore considered to be the first long-term treated patient with a combination of two types of ICIs. Our patient wished a treatment

option that would allow him to survive long-term while avoiding side effects as much as possible. Thus, considering the mildly decreased renal function, combination therapy with cytotoxic drugs was excluded. As a result, the Checkmate 227 regimen, which involves the administration of two ICIs rather than a single ICI, was chosen as his treatment. Due to this background, the initial doses of nivolumab and ipilimumab were not reduced. Thereafter, renal function tests were continued with great care, but there was no worsening, and as a result, the dose reduction of both drugs was not required in subsequent administrations. One year after the start of this treatment, PET/CT revealed residual disease only in the mediastinal lymph node behind the bifurcation, so irradiation was performed on this site. After completing this radiotherapy, the treatment was changed to nivolumab monotherapy, considering the impact on ICI treatment immediately after irradiation. After other 6 months, decreased thyroid function, which was considered to be an irAE, appeared, so thyroid hormone replacement therapy was started, and at the same time, administration of nivolumab was also discontinued. Thereafter, a follow-up has been conducted to check for any changes in the images, but no signs of recurrence have not been confirmed.

Conclusion

ICI therapy has brought about a revolutionary advance in the treatment of advanced NSCLC. Not a few patients with NSCLC have comorbid diseases. In patients who already have impaired renal function, particular attention must be paid to renal toxicity, a rare irAE. However, for advanced NSCLC patients with CKD, nivolumab and ipilimumab combination therapy might be one of the treatment options. It will be necessary to continue the research to verify and accumulate the data on the efficacy and safety of this treatment. We do believe that this report could provide some suggestions for the treatment of future patients who might experience a similar course of the therapy.

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Authors' contributions

HM and HS designed the study. HM, YM, GO, TS, HM and HS collected the data. HM and HS prepared the manuscript. All authors approved the final version for submission.

References

1. Gridelli C, Peters S, Mok T et al. Face to face among different chemo-immunotherapy combinations in the first line treatment of patients with advanced non-small cell lung cancer: results of an international expert panel meeting by the Italian association of thoracic oncology (AIOT). Lung Cancer 2024; 187: 107441. doi: 10.1016/j.lungcan.2023.107441.
2. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39 (2 Suppl 1): S1–S266.
3. Levey AS, Eckardt KU, Tsukamoto Y et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005; 67(6): 2089–2100. doi: 10.1111/j.1523-1755.2005.00365.x.
4. Kagamu H. Immunotherapy for non-small cell lung cancer. Respir Investig 2024; 62(2): 307–312. doi: 10.1016/j.resinv.2024.01.011.
5. Reck M, Schenker M, Lee KH et al. Nivolumab plus ipilimumab versus chemotherapy as first-line treatment in advanced non-small-cell lung cancer with high tumour mutational burden: patient-reported outcomes results from the randomised, open-label, phase III CheckMate 227 trial. Eur J Cancer 2019; 116: 137–147. doi: 10.1016/j.ejca.2019.05.008.
6. Ishizuka S, Sakata S, Yoshida C et al. Successful treatment by pembrolizumab in a patient with end-stage renal disease with advanced non-small cell lung cancer and high PD-L1 expression. Respir Investig 2018; 56(4): 361–364. doi: 10.1016/j.resinv.2018.03.005.
7. Sproat MR, Hofherr ML, Devarakonda S. Successful use of sotorasib in a patient with end-stage renal disease on dialysis with metastatic lung adenocarcinoma: a case report. Clin Lung Cancer 2022; 23(6): e339–e341. doi: 10.1016/j.cllc.2022.04.007.
8. Imai R, Kitamura A. Successful treatment with atezolizumab in a haemodialysis patient with large cell neuroendocrine carcinoma. Respirol Case Rep 2023; 11(8): e01193. doi: 10.1002/rcr2.1193.
9. Abraham S, Samson A. Case report: successful treatment of a patient undergoing haemodialysis with multifocal hepatocellular carcinoma using atezolizumab and bevacizumab. Front Oncol 2024; 13: 1279501. doi: 10.3389/fonc.2023.1279501.
10. Büchler T. Renal toxicity of cancer immunotherapy. Klin Onkol 2020; 33(1): 29–31. doi: 10.14735/amko202029.
11. Herz S, Höfer T, Papapanagiotou M et al. Checkpoint inhibitors in chronic kidney failure and an organ transplant recipient. Eur J Cancer 2016; 67: 66–72. doi: 10.1016/j.ejca.2016.07.026.
12. Kanz BA, Pollack MH, Johnpulle R et al. Safety and efficacy of anti-PD-1 in patients with baseline cardiac, renal, or hepatic dysfunction. J Immunother Cancer 2016; 4: 60. doi: 10.1186/s40425-016-0166-5.
13. Espi M, Teuma C, Novel-Catin E et al. Renal adverse effects of immune checkpoints inhibitors in clinical practice: ImmuNoTox study. Eur J Cancer 2021; 147: 29–39. doi: 10.1016/j.ejca.2021.01.005.
14. Hu R, Chen M, Xu Y et al. Renal immune-related adverse events of immune checkpoint inhibitor. Asia Pac J Clin Oncol 2020; 16(6): 305–311. doi: 10.1111/ajco.13387.
15. Herrmann SM, Perazella MA. Immune checkpoint inhibitors and immune-related adverse renal events. Kidney Int Rep 2020; 5(8): 1139–1148. doi: 10.1016/j.ekir.2020.04.018.
16. Seethapathy H, Zhao S, Chute DF et al. The incidence, causes, and risk factors of acute kidney injury in patients receiving immune checkpoint inhibitors. Clin J Am Soc Nephrol 2019; 14(12): 1692–1700. doi: 10.2215/CJN.00990119.
17. Isik B, Alexander MP, Manohar S et al. Biomarkers, clinical features, and rechallenge for immune checkpoint inhibitor renal immune-related adverse events. Kidney Int Rep 2021; 6(4): 1022–1031. doi: 10.1016/j.ekir.2021.01.013.
18. Manohar S, Ghamrawi R, Chengappa M et al. Acute interstitial nephritis and checkpoint inhibitor therapy: single center experience of management and drug rechallenge. Kidney360 2020; 1(1): 16–24. doi: 10.34067/KID.0000152019.
19. Cortazar FB, Kibbelaar ZA, Glezerman IG et al. Clinical features and outcomes of immune checkpoint inhibitor-associated AKI: a multicenter study. J Am Soc Nephrol 2020; 31(2): 435–446. doi: 10.1681/ASN.2019070676.
20. Mamlouk O, Selamet U, Machado S et al. Nephrotoxicity of immune checkpoint inhibitors beyond tubulointerstitial nephritis: single-centeer experience. J Immunother Cancer 2019; 7(1): 2. doi: 10.1186/s40425-018-0478-8.
21. Manohar S, Kompotiatis P, Thongprayoon C et al. Programmed cell death protein 1 inhibitor treatment is associated with acute kidney injury and hypocalcemia: meta-analysis. Nephrol Dial Transplant 2019; 34(1): 108–117. doi: 10.1093/ndt/gfy105.
22. Sorah JD, Rose TL, Radhakrishna R et al. Incidence and prediction of immune checkpoint inhibitor-related nephrotoxicity. J Immunother 2021; 44(3): 127–131. doi: 10.1097/CJI.0000000000000338.