

Incidence and Outcomes of Renal Adverse Events following Treatment with Immune Checkpoint Inhibitors

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Running Title: Immune checkpoint inhibitor renal outcomes

ABSTRACT

Aim: To determine the incidence of renal adverse events in patients treated with checkpoint inhibitors (CPI) and the outcomes of renal insufficiency events. To determine the risk factors predisposing patients to renal insufficiency in patients treated with CPI.

Design and methods: A prospective single arm cohort study was designed. All patients aged above 18 with solid organ malignancies starting therapy with CPI from April 2020 were observed at baseline and followed up for a period of one year. Patients with Chronic kidney disease (CKD) 4 and above were excluded. Demographic data, concurrent medical conditions, medications, malignancy type, CPI type were recorded at baseline and during follow up. Two renal physicians determined the aetiology of renal insufficiency as CPI related or unrelated. Univariate logistic regression was performed to identify patient characteristics associated with development of acute kidney injury (AKI). Kaplan-Meier was used to determine survival differences between those who did and did not develop AKI

Results: The incidence of CPI induced AKI was 2.9%. Multivariate analysis showed proton pump inhibitor (PPI) use to be associated with high risk of CPI induced all-cause AKI. There was a trend towards increased mortality in patients who developed all-cause AKI. However, there was no mortality in patients with CPI induced AKI.

Conclusion: Our single centre study showed that the incidence of renal insufficiency events is minimal in patients treated with CPI. PPI use increased risk of all-cause AKI in these patients. CPI associated AKI is not associated with increased mortality.

Keywords: Acute kidney injury; CTLA-4 antigen; Immune checkpoint inhibitors; Proton pump inhibitors; renal Insufficiency

Summary at a Glance: This prospective single arm cohort study identified the incidence of immune checkpoint inhibitor (CPI) induced AKI was 2.9%. Proton pump inhibitor (PPI) use was found to increase the risk of CPI induced AKI and there was a trend towards increased mortality in patients who developed AKI.

INTRODUCTION

Immune checkpoint inhibitors (CPIs) are monoclonal antibodies increasingly being used in the management of solid organ and haematological malignancies.¹⁻³ CPIs enhance the immune response by blocking immune checkpoints, most commonly cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1) and programmed cell death protein ligand 1 (PD-L1).^{1,3,4} CPI use is associated with the development of immune-related adverse events (IRAE), including renal IRAE.^{1,5,6} Information regarding risk factors for renal IRAE is limited. This highlights the need for investigation into predisposing factors such that patients at risk can be monitored and managed to prevent or reduce renal IRAE occurrence.^{7,8}

Renal IRAE are uncommon, where Cortazar et al reported a 2.2% incidence of CPI-related acute kidney injury (AKI) in patients on CPI monotherapy.¹ Acute interstitial nephritis (AIN) is the most common renal IRAE, however, disease manifestations are broad, including IgA nephropathy, membranous nephropathy and renal vasculitis.^{1,4,7,9,10} Kidney biopsy reveals marked T cell infiltration, establishing the key role of T cells in renal IRAE pathogenesis.^{5,11,12} Despite histological findings, the exact mechanism of renal IRAE is unknown. Murakami et al proposed CPI use enables activation of dormant autoreactive T cells that escaped thymic deletion resulting in selective kidney injury.¹³ Koda et al proposed an alternative hypothesis, suggesting CPI therapy disrupts the longstanding immunological tolerance to potentially nephrotoxic drugs, enabling immune attack on the kidney.¹⁴ However, renal IRAE development in select patients suggests these mechanisms interact further with patient-specific factors.

CPI-related AKI have variable clinical presentations, where Koks et al found patients presented with variable leukocyturia, haematuria and proteinuria and were otherwise asymptomatic.¹⁵ Furthermore, Izzedine et al determined the median time to onset of CPI-related AKI was nine months but presentation occurred between one- and twenty-four-months following CPI initiation.¹⁶ Most epidemiological information on renal IRAE development is currently formed from retrospective observational studies which have limited ability to detect asymptomatic and mild cases that develop outside of the data collected.^{16,17} Therefore, the limited information on the broad clinical patterns of renal IRAE emphasises the importance of active renal function monitoring in patients at risk of developing renal IRAE to ensure detection.

There is currently no standard treatment for renal IRAE, however, guidelines recommend CPI and concomitant nephrotoxic drug cessation and administration of corticosteroids.^{18,19} CPI-related AKI are not associated with increased patient mortality, however, tumour regrowth during CPI cessation period and partial or incomplete recovery of kidney function have been observed.^{15,17,19} Therefore, it is important to identify high risk patients with predisposing demographic features, medications, comorbidities, cancer type and CPI type to guide monitoring and management of at risk patients in a clinical setting to prevent or reduce renal IRAE occurrence to ensure CPI therapy can continue.

The study aimed to identify the incidence and outcomes of renal IRAE in cancer patients following initiation of CPI therapy.

MATERIALS AND METHODS

Ethics Statement

The research study was approved by the Nepean Blue Mountains Local Health District Human Research Ethics Committee, ethics approval #2020/ETH00076.

Study Design and Patient Population

The current study is a prospective observational single arm cohort study involving patients with solid organ and haematological malignancies who initiated CPI therapy from the 1st of April 2020 to the 1st of April 2021 at the Nepean Cancer Care Centre. The study involved collection of baseline data prior to CPI therapy and visit data following commencement of CPI therapy. Participants who commenced CPI therapy between the 1st of April 2020 and the 1st of March 2021 were followed for twelve months and participants who commenced therapy from the 2nd of March 2021 to the 1st of April 2021 were followed for eleven months.

Inclusion criteria required participants to be aged eighteen years and above and attend Nepean Cancer Care Centre and/or be admitted to Nepean Hospital to receive CPI therapy for malignancy management. The study excluded patients with chronic kidney disease (CKD) stage 4 and above and patients on dialysis. Participants were identified through Nepean Cancer Care Centre pharmacy.

Data collection and Outcome Definitions

Participant data was collected by medical student from paper medical records and electronic medical records accessed through PowerChart and Mosaiq systems. Data was de-identified and stored in RedCap. Data collected at baseline and for visits is summarised in Table 1. The primary outcome was the incidence of AKI and CKD due to CPI and non CPI related causes. The secondary outcome of the study examined the one-year survival with and without renal impairment following treatment.

Data analysis

The incidence of AKI and CKD was determined by medical student. The aetiology of the AKI and CKD were determined as CPI or non-CPI related by two renal physicians. (The criteria for determining CPI induced AKI was based on the presence of new onset proteinuria or leucocyturia and the absence of any other precipitating event for AKI including sepsis, prerenal causes and other nephrotoxic medications) A comparison between participants who did and did not develop AKI was performed. Baseline characteristics were presented as means and standard deviations for normally distributed continuous variables, medians and interquartile range for non-normally distributed continuous variables and counts and percentages for categorical variables. Normally distributed variables were determined by skewness on a histogram. Univariate logistic regression was performed to identify patient characteristics associated with development of AKI. Univariate cox proportional hazard model was used to identify factors influencing time to AKI development. Multivariate logistic regression and multivariate

cox proportional hazard model was performed a priori using significant findings from literature; PPI, NSAID, sex, age and CPI agent, and using characteristics with p-value <0.25 from univariate analysis.^{5,7,9,14,20-23} Kaplan-Meier was used to determine survival differences between those who did and did not develop AKI and those who developed CPI-induced AKI and non-CPI-induced AKI. Data analysis was performed using SPSS version 27.

RESULTS

3.1 Baseline characteristics

A total of 105 patients with solid organ or haematological malignancies were included in the study. The baseline characteristics of the participants are summarised in Table 3. The mean age of participants was 67.3 ± 10.7 years, 62.9% were male and 90.5% were Caucasian (Table 1). The median baseline creatinine and eGFR were 75.0 (61.5-90.0) $\mu\text{mol/L}$ and 84.0 (68.5-90.0) mL/min/1.73m^2 , respectively, and no patients had proteinuria at baseline. Hypertension (44.8%) and ACEi/ARBs (34.3%) were the most common underlying medical condition and medication used at baseline, respectively. Lung cancer (56.2%) was the most prevalent malignancy type followed by melanoma (17.1%) and head and neck malignancy (7.6%). Monotherapy was the most common where PD-1 agents were used by 60.9% of participants and pembrolizumab (38.1%) was the most used CPI agent, followed by combination nivolumab/ipilimumab (16.2%) (Table 3). Total underlying medical conditions and medications prior to first AKI are shown in Appendix 1.

3.2 Incidence and outcomes of AKI, CKD and proteinuria

A total of 26 (24.8%) participants developed at least one AKI over the eleven-twelve-month follow-up period (Table 3). Complete recovery occurred in 17 (65.4%) patients with AKI, partial recovery occurred in 6 (23.1%) and data was unavailable in 3 (11.5%) patients. The median time to development of the first AKI was 12 (5.8-33.8) weeks with a range of 0 to 51 weeks from baseline. Of the 26 participants who developed AKI, 3 (11.5%) developed CPI-related AKI, leading to an overall incidence of CPI-related AKI of 2.9% (Table 3). Complete recovery occurred in 1 (33.3%) of patients and 2 (66.7%) did not recover. The median time to development of CPI-related AKI was 8 weeks with a range of 8 to 14 weeks. Interquartile range for time to development of CPI-related AKI could not be calculated due to small population size.

New-onset CKD occurred in 2 (1.9%) participants and new-onset proteinuria occurred in 4 (3.8%) participants. The mean time to development of CKD and proteinuria was 22 weeks (range 21-23) and 7 (3.5-10) weeks, respectively. Of the 2 patients who developed new-onset CKD, 1 (50%) was found to have CPI-related CKD, leading to an overall incidence of 1.0%. This case developed 21 weeks from the onset of CPI therapy.

A total of 71 MSUs were performed over the twelve-month period, where 20 (28.2%) confirmed haematuria and 35 (49.3%) confirmed leukocyturia. Of the 26 participants who developed AKI, 4 (16%) had haematuria, 5 (20%) had leukocyturia and 1 (4%) had proteinuria associated with the event. Haematuria and

leukocyturia were not significantly associated with AKI in patients tested, with p-values of 1.00 and 0.46, respectively, from Fisher-exact test.

3.3 Risk factors for AKI

A univariate logistic regression of patients with AKI showed no significant association between AKI and patient characteristics (Table 4). PPI was found to be slightly non-significant with HR 2.86 (CI 95% 0.98-8.4), p-value 0.06 (Table 4). Multivariate logistic regression found PPI to be significant with HR 3.04 (CI 95% 0.99-9.33), p-value 0.05 (Table 5), in causing all-cause AKI. Of the 3 participants who developed CPI-related AKI, the mean age was 70.0 ± 6.5 years and 100% were male and Caucasian. Diabetes and NSAID use were present in 1 (33.3%) participant each, respectively. Melanoma was the predominant malignancy (66.7%) followed by lung cancer (33.3%). PD-1 agents were taken by 2 (66.7%) participants, pembrolizumab and nivolumab, and a PD-L1 agent was taken by 1 (33.3%) patient, atezolizumab (Table 3).

Among patients who developed all-cause AKI, univariate and multivariate Cox proportional hazard test did not identify any significant factors contributing to time to development of AKI (Table 6 and 7). PPI was found to be slightly non-significant with HR 2.41 (CI 95% 0.91-6.40), p-value 0.08, and HR 2.52 (CI 95% 0.92-6.91), p-value 0.07, for univariate and multivariate analysis respectively (Table 6 and 7).

No significant factors were identified on multivariate logistic regression and multivariate Cox proportional hazard test a priori (Appendix 2 and 3).

3.4 Mortality

Of the 105 participants, 73.0 (69.5%) survived and 32.0 (30.5%) died during the eleven-twelve-month follow-up period. The median time to death was 24.5 (14.3-32.0) weeks. In patients with AKI, 15 (60%) survived and 10 (40%) died during the eleven-twelve-month follow-up period. All 3 patients with CPI-related AKI survived the eleven-twelve-month follow-up period. Cox proportional hazard model showed no significant difference in survival for patients with and without AKI, p-value 0.21 (Figure 1). Similarly, no significant difference was observed in survival of patients with and without CPI-related AKI, p-value 0.20 (Figure 2).

DISCUSSION

The current study investigated 105 patients with solid organ and haematological malignancies who received CPI therapy over an eleven-twelve-month period to determine the incidence and identify risk factors of renal IRAE. CPI-related AKI was observed in 2.9% of patients, correlating with existing findings of 2-5% incidence.^{1,17,24,25} The current study did not observe a significant association between CPI agent and development of AKI. All patients who developed CPI-related AKI received monotherapy, contrasting previous studies which observed higher incidence of AKI in patients on combined agent therapy.^{1,20,24} The discrepancy can be attributed to the present study not being powered to determine the association between patient characteristics and incidence of AKI due to the small participant number. Additionally, the median time to CPI-related

AKI onset was earlier than all-cause AKI at 8 and 12 weeks, respectively. Isik et al similarly reported significantly earlier onset of CPI-related AKI compared to non-CPI-induced AKI, at 4 and 8.5 months respectively, suggesting earlier onset AKI during treatment is more likely to be CPI-related.²⁶

Previously reported risk factors for AKI include older age, male sex, low baseline eGFR, NSAIDs, PPIs and combination nivolumab/ipilimumab CPI therapy.^{5,7,9,14,20-23} The current study identified PPI use (p-value 0.05) significantly increased the risk of all-cause AKI on multivariate analysis. The association of PPI use with AKI during CPI treatment is well documented.^{5,7,14,17,27} Koda et al explains this association by suggesting CPIs disrupt immunological tolerance to potentially nephrotoxic drugs, like PPIs, enabling attack of kidney tissue.¹⁴ Additionally, PPI use was found to be just outside the level of significance for association to time of development of AKI. Further investigation with a larger study population is required to determine the significance as there is limited investigation into factors influencing time to AKI onset. Currently, Chen et al identified type of CPI agent is significant in time to AKI, however, other studies have not observed significance.^{20,26}

Atezolizumab and cemiplimab monotherapy were found to trend towards increased risk of AKI development on univariate analysis. Atezolizumab has previously been identified by Chen et al to have the highest association with renal IRAE compared to other CPI monotherapies in a 10-year real-world pharmacovigilance study, however, the present study would require a larger number of participants to determine significance.²⁰ Furthermore, due to the small population size, the current study was limited to examination of risk factors for all-cause AKI and unable to identify characteristics associated with CPI-related AKI.

The present study identified a trend towards increased mortality in patients who developed AKI which correlates with existing findings where Koks et al identified a 2.13-fold increase in mortality with all-cause AKI.¹⁵ This could be due to poorer general health of the patients and underlying medical conditions. Additionally, the current study observed a trend towards increased survival in patients with CPI-related AKI compared to non-CPI-related AKI. This association can be attributed to IRAE being a manifestation of effective immune activation by CPI therapy and thus, associated with improved survival.²⁸⁻³⁰ A larger sample size is required to elucidate this significance as many studies have not reported improved survival with renal IRAE.^{15,24,25} However, Koks et al observed no increased risk of mortality in patients with CPI-related AKI and previous studies have shown improved survival and enhanced anti-tumour response with development on non-renal IRAE.^{15,29,30} Further, Patel et al observed a prolonged response to CPI therapy in renal cell carcinoma patients with renal IRAE, suggesting renal IRAE were associated with improved oncological outcomes and therefore, better survival.²⁸ Although, the improved outcomes were attributed to shared antigenic epitopes between normal and RCC renal tissue and therefore, may not be applicable to different cancer types.²⁸

The small participant number was the main limitation of this study, preventing analysis of AKI-, CKD- and proteinuria-related events. Further, a larger population would power the study to detect all significant risk factors associated with AKI development. Kidney biopsy was not performed to confirm suspected CPI-related AKI and therefore, incidence may be over-estimated. However, the current study is beneficial as a scoping study for renal IRAE and forms the foundation for a future multicentre study with a larger study population. Due to the waiver of consent, there was no recruitment bias, enabling inclusion of all patients who met the inclusion criteria. The prospective nature of the study also enabled all available patients to be followed over the eleven-twelve-month period.

CONCLUSION

There is limited evidence of risk factors for renal IRAE and variable reports of incidence. The current single-centre study determined the incidence of renal IRAE and identified PPI use as a risk factor for all-cause AKI in patients on CPIs. The study identified a trend for increased mortality with all-cause AKI and improved survival in patients with CPI-related AKI. In the future, a larger multi-centre observational study would be performed to provide further evidence regarding the incidence and outcomes of CPI-related AKI. This would enable identification of at-risk patients to ensure appropriate monitoring and management of predisposed patients throughout CPI therapy.

DECLARATIONS

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Conflicts of Interest

The authors declare that there are no conflicts of interest with the present study.

REFERENCES

1. Cortazar FB, Marrone KA, Troxell ML, et al. Clinicopathological features of acute kidney injury associated with immune checkpoint inhibitors. *Kidney international*. 2016;90(3):638-647.
2. Eggermont AMM, Chiarion-Sileni V, Grob J-J, et al. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. *The New England journal of medicine*. 2016;375(19):1845-1855.
3. Wanchoo R, Karam S, Uppal NN, et al. Adverse Renal Effects of Immune Checkpoint Inhibitors: A Narrative Review. *American journal of nephrology*. 2017;45(2):160-169.
4. Bajwa R, Cheema A, Khan T, et al. Adverse Effects of Immune Checkpoint Inhibitors (Programmed Death-1 Inhibitors and Cytotoxic T-Lymphocyte-Associated Protein-4 Inhibitors): Results of a Retrospective Study. *Journal of clinical medicine research*. 2019;11(4):225-236.
5. Espi M, Teuma C, Novel-Catin E, et al. Renal adverse effects of immune checkpoints inhibitors in clinical practice: ImmuNoTox study. *European journal of cancer (1990)*. 2021;147:29-39.
6. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. *The New England journal of medicine*. 2018;378(2):158-168.

7. Mamlouk O, Selamet U, Machado S, et al. Nephrotoxicity of immune checkpoint inhibitors beyond tubulointerstitial nephritis: single-center experience. *Journal for immunotherapy of cancer*. 2019;7(1):2-2.
8. Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *Journal for immunotherapy of cancer*. 2017;5(1):95-95.
9. Gupta S, Short SAP, Sise ME, et al. Acute kidney injury in patients treated with immune checkpoint inhibitors. *Journal for immunotherapy of cancer*. 2021;9(10):e003467.
10. Mitarai Y, Nakashima K, Fukunaga S, et al. IgA Nephropathy that Developed as an Immune-related Adverse Event of Pembrolizumab Complicated with Interstitial Nephritis: A Case Study. *Internal medicine (Tokyo, 1992)*. 2022:7115-7121.
11. Okawa S, Fujiwara K, Shimonishi A, et al. Rapidly Progressive Acute Kidney Injury Associated with Nivolumab Treatment. *Case reports in oncology*. 2020;13(1):85-90.
12. Tabei A, Watanabe M, Ikeuchi H, et al. The Analysis of Renal Infiltrating Cells in Acute Tubulointerstitial Nephritis Induced by Anti-PD-1 Antibodies: A Case Report and Review of the Literature. *Internal medicine (Tokyo, 1992)*. 2018;57(21):3135-3139.
13. Murakami N, Borges TJ, Yamashita M, Riella LV. Severe acute interstitial nephritis after combination immune-checkpoint inhibitor therapy for metastatic melanoma. *Clinical kidney journal*. 2016;9(4):649-649.
14. Koda R, Watanabe H, Tsuchida M, et al. Immune checkpoint inhibitor (nivolumab)-associated kidney injury and the importance of recognizing concomitant medications known to cause acute tubulointerstitial nephritis: A case report. *BMC nephrology*. 2018;19(1):48-48.
15. Koks MS, Ocak G, Suelmann BBM, et al. Immune checkpoint inhibitor-associated acute kidney injury and mortality: An observational study. *PloS one*. 2021;16(6):e0252978-e0252978.
16. Izzedine H, Mathian A, Champiat S, et al. Renal toxicities associated with pembrolizumab. *Clinical kidney journal*. 2019;12(1):81-88.
17. Seethapathy H, Zhao S, Chute DF, et al. The incidence, causes, and risk factors of acute kidney injury in patients receiving immune checkpoint inhibitors. *Clinical journal of the American Society of Nephrology*. 2019;14(12):1692-1700.
18. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. *Journal of clinical oncology*. 2018;36(17):1714-1768.
19. Zheng K, Qiu W, Wang H, et al. Clinical recommendations on diagnosis and treatment of immune checkpoint inhibitor-induced renal immune-related adverse events. *Thoracic cancer*. 2020;11(6):1746-1751.
20. Chen G, Qin Y, Fan Qq, Zhao B, Mei D, Li Xm. Renal adverse effects following the use of different immune checkpoint inhibitor regimens: A real-world pharmacoepidemiology study of post-marketing surveillance data. *Cancer medicine (Malden, MA)*. 2020;9(18):6576-6585.
21. Cortazar FB, Kibbelaar ZA, Glezerman IG, et al. Clinical features and outcomes of immune checkpoint inhibitor-associated AKI: A multicenter study. *Journal of the American Society of Nephrology*. 2020;31(2):435-446.
22. Haeuser L, Marchese M, Cone EB, et al. Nephrotoxicity of immune checkpoint inhibitor therapy: a pharmacovigilance study. *Nephrology, dialysis, transplantation*. 2021.
23. Qu J, Ding Y, Jiang K, et al. Nephrotoxicity of Immune Checkpoint Inhibitors: A Disproportionality Analysis from 2013 to 2020. *Tohoku journal of experimental medicine*. 2021;254(4):275-282.
24. Abdelrahim M, Mamlouk O, Lin H, et al. Incidence, predictors, and survival impact of acute kidney injury in patients with melanoma treated with immune checkpoint inhibitors: a 10-year single-institution analysis. *Oncoimmunology*. 2021;10(1):1927313-1927313.
25. Shimamura Y, Watanabe S, Maeda T, Abe K, Ogawa Y, Takizawa H. Incidence and risk factors of acute kidney injury, and its effect on mortality among Japanese patients receiving immune check point inhibitors: a single-center observational study. *Clinical and experimental nephrology*. 2021;25(5):479-487.
26. Isik B, Alexander MP, Manohar S, et al. Biomarkers, Clinical Features, and Rechallenge for Immune Checkpoint Inhibitor Renal Immune-Related Adverse Events. *Kidney international reports*. 2021;6(4):1022-1031.
27. Kato K, Mizuno T, Koseki T, et al. Concomitant proton pump inhibitors and immune checkpoint inhibitors increase nephritis frequency. *In vivo (Athens)*. 2021;35(5):2831-2840.
28. Patel V, Elias R, Formella J, et al. Acute interstitial nephritis, a potential predictor of response to immune checkpoint inhibitors in renal cell carcinoma. *Journal for immunotherapy of cancer*. 2020;8(2).
29. Riudavets M, Barba A, Maroto P, et al. Correlation between immune-related adverse events (irAEs) and efficacy in patients with solid tumors treated with immune-checkpoints inhibitors (ICIs). *Journal of clinical oncology*. 2018;36(15_suppl):3064-3064.
30. Rogado J, Sánchez-Torres JM, Romero-Laorden N, et al. Immune-related adverse events predict the therapeutic efficacy of anti-PD-1 antibodies in cancer patients. *European journal of cancer (1990)*. 2019;109:21-27.