Acute Kidney Injury in Patients Treated With Immune Checkpoint Inhibitors : A Retrospective Real-World Study

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Abstract

Background Immune checkpoint inhibitors (ICPi) have advanced cancer treatment. However, data from the past decade has highlighted the risk of immune-related side effects and ICPi – associated acute kidney injury (AKI). We aimed to compare the epidemiology of ICPi-associated AKI and AKI not directly related to ICPi's in patients receiving ICPi therapy.
Methods This was a single-centre, retrospective analysis of all cancer patients who received ICPi therapy between December 2011 and August 2020 in a tertiary cancer center in the UK. The primary outcome was overall mortality. Secondary outcomes were the incidence of ICPi-AKI and AKI due to other causes, risk factors, and kidney outcomes up to 1 year after AKI diagnosis.
Results The cumulative incidence of any AKI was 13.2%, and ICPi-AKI was 3.1%. CKD was a risk factor for ICPi-AKI and ICPi-AKI patients had a lower chance of complete kidney recovery. In fact, the prevalence of CKD at one year after ICPi-AKI was higher than other types of AKI (62% and 38%, respectively) . However, early steroid prescription was associated with complete AKI recovery (p = 0.006). Recurrent AKI was found in 41% of those rechallenged with ICPi. Compared with no-AKI, ICPi-AKI was not associated with an increased mortality risk.
Conclusions The risk of AKI in cancer patients treated with ICPi therapy was 13%. ICPi-AKI was less common but associated with a higher risk of CKD at 1 year than AKI from other causes.

Keywords Immune checkpoint inhibitors, immunotherapy, acute kidney injury

Introduction

Since their introduction two decades ago, immune checkpoint inhibitors have revolutionized cancer treatment. Nevertheless, these monoclonal antibodies have also been implicated in immune-related adverse events (irAEs) as a result of their role in enhancing tumour-directed immune responses. IrAEs are reported at an incidence ranging from 60% to 85%, with renal complications presenting with acute kidney injury or glomerulonephritides. We, therefore, sought to compare the epidemiology of AKI associated with ICPi and those unrelated to ICPi therapy in patients receiving ICPi therapy in this study.

Methods and Materials

This was a retrospective analysis of all cancer patients who received ICPi therapy between December 2011 and August 2020 in a tertiary cancer center in the UK. AKI was defined by the KDIGO criteria and ICPi-associated AKI (ICPi-AKI) was determined using the Gupta/Leaf classification. Clinical data were obtained from electronic medical records. These include baseline demographic data, comorbidities, medications and laboratory values at ICPi initiation. In addition, types and staging of malignancy, class of ICPi used, concurrent chemotherapy, the incidence of extrarenal adverse events, disease and survival outcomes at one year were also obtained. Out of 1351 patients identified, 1039 were enrolled. Patients were then identified for AKI and no AKI (Figure 1), and subsequent sub-analyses comparing overall survival and kidney outcome were performed comparing ICPi-AKi vs other AKI.

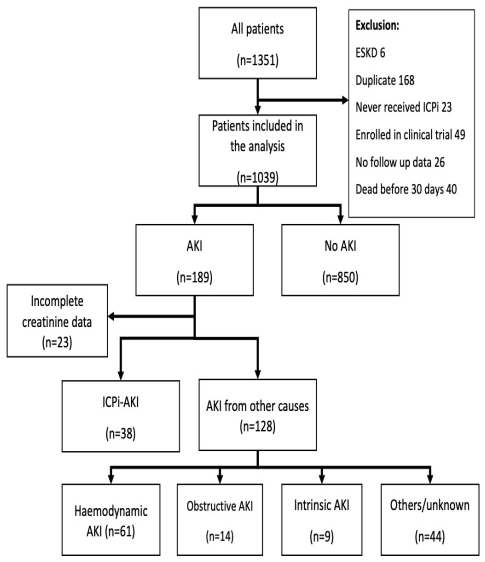

Figure 1 : Flow chart of patient inclusion and exclusion

Results

A total of 1039 patients were included in the study. The mean age was 58, with 60% male and 22% had CKD. Those with ICPi-AKI had lower eGFR at baseline (mean 62.5 ml/min/1.73m^2) as compared to those without AKI and AKI of other causes (mean 81.9 and 87.7 ml/min/1.73m^2, respectively). CKD was a risk factor for ICPi-AKI (HR 2.53, 95% CI 1.27-5.04, p=0.009). Cumulative incidence for all types of AKI is 13.2% and ICPi AKI is 3%. (Figure 2) Among those with AKI, all ICPi-AKI had persistent AKI as compared to 66% with other AKI (p < 0.0001). 1/4 had their ICPi held at various stages of AKI, of which only 2.4% were biopsied. 41% out of those rechallenged after their ICPi held developed recurrent AKI (p=0.222). Almost all diagnosed with ICPi-AKI received steroids for AKI (p <0.0001) with time to steroids initiation was within the first seven days. ICPi-AKI patients had the highest peak of SCr at diagnosis (262 umol/l) as compared to other AKI (peak at 144 umol/l). (Figure 3) They also had the lowest chance of complete renal recovery at 1 year compared to non-ICPi AKI (in survivors) (53% vs 78%, p 0.009). The overall survival was not significantly different between ICPi-AKI, other AKI and those without AKI (log rank p = 0.084). (Figure 4)

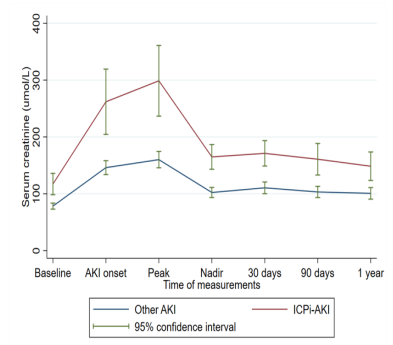

Figure 3. Creatinine changes in ICPi AKI vs other AKI

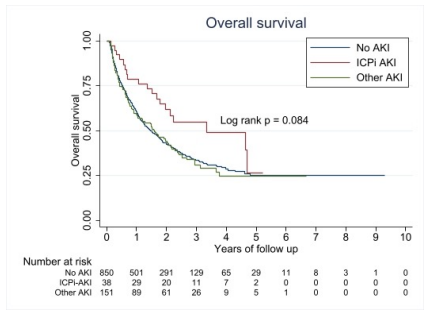

Figure 4. Overall survival after ICPi initiation adjusted by age, AKI staging, kidney recovery and disease progression

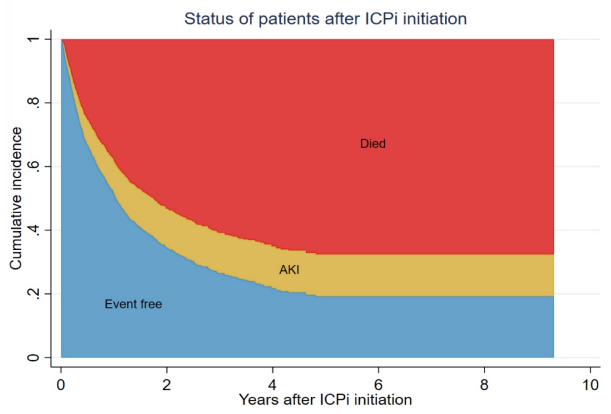

Figure 2. Cumulative AKI incidence after ICPi initiation accounted for competing risk of death

Discussion

Our single-centre study found that CKD was a risk factor for ICPi AKI, in agreement with previous research. Patients with ICPi AKI were also noted to have more severe AKI, as evidenced by a higher peak creatinine level at diagnosis. As a result, this could lead to a lower chance of complete renal recovery due to a more extensive irreversible insult secondary to an exaggerated immune response caused by the drug. Interestingly, our analysis of those with ICPi-AKI does not suggest an increased risk in mortality, but further analyses are necessary to confirm these findings. There is a need for more studies to evaluate whether steroid directly affects mortality and kidney recovery in patients with ICPi AKI to confirm these findings.

Conclusions

In cancer patients treated with ICPi therapy, the risk of AKI was 13%. ICPi-AKI was less common but associated with a higher risk of CKD at 1 year than AKI from other causes. There was no difference in mortality between both groups.

Disclosures and Acknowledgement

*Nurul Z Nordin is an AKI Ravi-Mehta ISN (International Society of Nephrology) Fellow and this work was made possible during her ISN-funded fellowship in Critical Care Nephrology at Guy's & St Thomas' Hospital, London, United Kingdom.
*Nurul Z Nordin, Pietro Vassalo, Nina Seylanova, Natasha Lewis, Abigail Hobill, Luke Martin, Kittisak Weerapolchai contributed equally to this work.
*Graphics by Nuttha Lumlertgul and both Nuttha Lumlertgul and Marlies Ostermann are senior authors.