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ORIGINAL ARTICLE

Combination therapy with immune check point inhibitors and acute kidney injury

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ABSTRACT

Background: Immune checkpoint inhibitors have revolutionized the treatment of metastatic renal cell carcinoma and malignant melanoma but are also associated with a risk of severe side effects. Nephrotoxicity is an immune checkpoint inhibitor-related adverse effect, but acute kidney injury (AKI) can also be caused by other more common conditions. This study aimed to describe the incidence and causes of AKI in patients treated with combination therapy of immune checkpoint inhibitors.

Material and methods: This retrospective cohort study included 200 patients receiving ipilimumab and nivolumab for either metastatic renal cell carcinoma or malignant melanoma at the Department of Oncology at Copenhagen University Hospital, Herlev between 1 January 2019 and 31 December 2020. The incidence and cause of AKI within 6 months after treatment was determined.

Results: In the 96 patients treated for malignant melanoma 15 patients (16%) had an episode of AKI. Two of these patients had potential immune checkpoint inhibitor-related AKI both of which received treatment with a proton pump inhibitor (PPI).Of the 104 included patients with metastatic renal cell carcinoma 26 patients (25%) developed AKI. Five of these patients had potential immune checkpoint inhibitor-related AKI. Treatment with PPI before the development of AKI occurred in 4 out of these 5 patients.

Conclusion: Patients receiving combination therapy with checkpoint inhibitors are at high risk of AKI, but different causes of AKI should always be considered. Use of PPI concurrently with ICIs is likely to increase the risk of AKI.

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Background

Immune checkpoint inhibitors (ICIs) represent major progress in modern oncology therapy. The use of ICIs both as single and combination therapy increases, and a thorough investigation of both effects, as well as side effects in all groups of patients receiving treatment with ICIs, is important.

ICI-related nephrotoxicity is not as common as other immune-related adverse effects. However, the incidence increases notably when prescribing combination ICI therapy reaching up to 4.9% in some studies [1].

Acute kidney injury (AKI) can be caused by ICI treatment, but also by other intercurrent events in this group of patients such as dehydration and infections.

The present study aimed to describe the incidence of AKI in a cohort of patients receiving combination therapy with ICIs and explore the frequency of the different causes of AKI.

Material and methods

This study was a retrospective observational cohort study (EQUATOR STROBE guideline followed for cohort studies) of patients receiving combination therapy with immune checkpoint inhibitors for either metastatic renal cell carcinoma (RCC) or malignant melanoma (MM) at the Department of Oncology at Copenhagen University Hospital, Herlev. Patients included received combination therapy with ipilimumab (CTLA4 inhibitor) and nivolumab (PD-1 inhibitor) at least one time between 1 January 2019 and 31 December 2020.

This study was embedded in a larger quality assurance study at Herlev Hospital aimed to record the number of patients receiving treatment with ICIs and patient outcomes related to therapy with ICIs.

Dates of administration of ICIs, laboratory data and a list of medications were obtained from patient files along with diagnosis codes for cancer type and chronic diseases.

The study was approved by the legal department at Herlev hospital (Workzone no.20024660).

Laboratory data routinely obtained from all patients before and during treatment with ICIs was available to determine baseline creatinine and changes in kidney function after treatment was initiated.

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Baseline creatinine was defined as plasma-creatinine measured before administration of the first treatment either on the day or the closest timely relation prior to the day of the first treatment.

Both Chronic kidney disease (CKD) and AKI were defined in accordance with KDIGO criteria. KDIGO (Kidney Disease Improving Global Outcomes) is a global organization developing and implementing evidence-based clinical practice guidelines in kidney disease [2].

CKD was defined as structural kidney damage or glomerular filtration rate (GFR) $<$60 mL/min/1.73 m2 for 3 months or more in accordance with KDIGO criteria [3].

AKI was defined using the KDIGO clinical practice guidelines [4] based on p-creatinine levels where AKI is defined as a rise of $\geq$26mmol/l or 0.3 mg/dl within 48 h or 50–99% rise in creatinine from baseline within 7 days.

We initially detected the patients with a rise of $\geq$26 μmol/L in p-creatinine or a 1.5 times increase in p-creatinine level. To minimize the influence of singular fluctuations in p-creatinine, AKI was defined if at least two consecutive measurements of p-creatinine met these criteria. Patients requiring initiation of renal replacement therapy were also defined as having AKI.

The number of patients with AKI within a 6-month period after receiving combination therapy with ICIs was determined and their records were examined to determine the cause of AKI.

Causes of AKI were divided into five categories: Prerenal kidney failure, Potential checkpoint inhibitor-related AKI, Nephrectomy, Unexplained AKI/undetermined cause of AKI and Postrenal AKI.

The NCI Common Terminology Criteria for Adverse Events (CTCAE) was applied to assess the severity of the loss of kidney function [5].

Results

A total of 200 patients received combination immunotherapy with ipilimumab and nivolumab for either metastatic RCC ($n = 104$) or MM ($n = 96$).

In 31 (32%) of the 96 patients treated for MM, at least one increased measurement of p-creatinine was observed. Only 15 patients (16%) had two consecutive measurements of p-creatinine meeting our definition of AKI.

The causes of AKI are shown in Table 1. Two patients had potential ICI-related AKI, CTCAE grade 2 and 3 respectively (graded using baseline p-creatinine). The interval from the initiation of ipilimumab and nivolumab to the occurrence of ICI-related AKI was 50 days and 84 days respectively. Both patients received treatment with high doses of methylprednisolone with significant improvement of kidney function, but some degree of chronic kidney disease remained in both (CKD stage 2 and 4 respectively). One of these patients underwent a kidney biopsy showing acute interstitial nephritis. This patient had a relapse of ICI-related AKI 11 months after receiving treatment with ipilimumab and nivolumab. This also responded with a partial remission to methylprednisolone treatment (Figure 1). None of the patients was treated with second-line immunosuppressive drugs. The other patient with potential ICI-related AKI in this group experienced a relapse with increasing p-creatinine while still treated with low-dose glucocorticoids for an ICI–related AKI. This responded to an increased dose of glucocorticoids and a prolonged treatment period. Blood samples revealed a slightly elevated eosinophil count in the patient.

None of the patients required treatment with dialysis and there were no cases of prior CKD in this group. Treatment with a PPI was present in 10/15 patients before the development of AKI including both patients classified in this study as potential ICI-related AKI (62% in non-ICI-related AKI versus 100% in ICI-related AKI). No patients in this group received treatment with a non-steroidal anti-inflammatory drug (NSAID).

Seven patients received treatment with glucocorticoids prior to changes in kidney function due to different reasons (adrenal insufficiency, cytokine release syndrome, colitis, skin condition, hepatitis, intracranial metastasis).

One patient received methylprednisolone upon admission due to suspicion of ICI–related AKI which was later abandoned and is classified in this study as a prerenal cause of AKI.

In 40 (39%) of the 104 included patients with metastatic RCC a single increase in p-creatinine occurred. Twenty-six (25%) had two consecutive increased measurements of p-creatinine. Eight patients suffered from moderate CKD prior to treatment (CKD stage 3 A, GFR 45-59 ($n = 7$) and CKD stage 3b, GFR 30–44 ($n = 1$)). The causes of AKI are described in Table 1. None of these patients underwent kidney biopsy. One patient required dialysis. Five patients had potential ICI-related AKI, three of which had a CTCAE grade 3 and two with a CTCAE 4 toxicity (graded using baseline p-creatinine). The interval from the initiation of ipilimumab and nivolumab to the occurrence of AKI ranged from 9 to 158 days (an average of 75 days). The five patients with potential ICI–related AKI received treatment with high doses of methylprednisolone resulting in dramatically improved kidney function, but four patients subsequently suffered from CKD (CKD stage 2 ($n = 1$) CKD stage 3a ($n = 1$) CKD stage 3b ($n = 2$)). One of these patients had already CKD stage 3a prior to treatment. None of the patients was treated with second-line immunosuppressive drugs.

Only one patient with potential ICI-related AKI had an elevated eosinophil count.

PPI treatment initiated before the development of AKI, occurred in 13 out of 26 patients (50%) who developed AKI, and in 4 out of the 5 patients (80%) with potential ICI-related AKI. Two patients received treatment with an NSAID, one of which had potential ICI-related AKI.

None of the patients with potential ICI-related AKI received treatment with glucocorticoids prior to their AKI. In addition to the five cases of potential ICI-related AKI, two patients were given a glucocorticoid upon hospital admission coincident with their AKI (colitis and intracranial metastases).

In total, we found seven cases of ICI-related AKI in this study. All patients with potential ICI-related AKI received treatment as instructed in regional guidelines in accordance

Table 1. Incidence of Acute kidney injury and patient characteristics.

Total $N = 200$		Metastatic renal cell carcinoma $N = 104$	Malignant melanoma $N = 96$
Patients with AKI*	41 (21%)	26 (25%)	15 (16%)
Causes of AKI			
Prerenal	16 (39%)	8 (31%)	8 (53%)
Potential ICI–related	7 (17%)	5 (19%)	2 (13%)
Nephrectomy	3 (7%)	3 (12%)	0
Unexplained	14 (34%)	10 (39%)	4 (27%)
Postrenal	1 (2%)	0	1 (7%)
CTCAE grade (number of patients)**			
Grade 1	15	12	3
Grade 2	17	8	9
Grade 3	7	4	3
Grade 4	2	2	0
Gender (number of men)	28 (68%)	21 (81%)	7 (47%)
Age (years (range))	64 (28–80)	59 (28–74)	58.3 (28–74)
CKD (number of patients)***	8 (20%)	8 (31%)	0
Other checkpoint inhibitor-related side effect	12 (29%)	7 (27%)	5 (33%)

AKI: Acute kidney injury; CTCAE: common terminology criteria for adverse events; CKD: Chronic kidney disease.
*AKI was defined using the KDIGO clinical practice guidelines along with two consecutive increasing measurements of se-creatinine within 6 months after receiving their last dose of combination therapy with ICIs.
**CTCAE was applied using baseline p-creatinine.
***KDIGOs definition: Kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for at least 3 months.

with international guidelines and were treated with methylprednisolone 1–2 mg/kg/day intravenously. Upon remission, patients were switched to prednisolone tablets. Treatment was slowly tapered alongside close monitoring of kidney function [6].

The number of patients with AKI with other checkpoint-inhibitor-related side effects is shown in Table 1. We did not find some side effects to be more frequent with AKI. Our data showed a broad spectrum of organ-related side effects including colitis, hepatitis, hypophysitis and thyroiditis.

Patients labeled as having unexplained causes of AKI were predominantly mild cases of AKI with quick spontaneous remission or in two cases patients who were admitted with immune-related hepatitis at the same time as their AKI. The causality was unclear and remission occurred before the clinicians involved found it necessary to do more than monitor the se-creatinine.

Discussion

In the present study, AKI occurred within 6 months in 25% of patients with metastatic RCC and 16% of patients with MM treated with combination ICIs.

In addition, we found a surprisingly high incidence (32% and 39%) of patients with a single increase in p-creatinine which could be classified as AKI according to the KDIGO clinical practice guidelines. This may reflect changes in the hydration status and is only followed by a sustained increase in p-creatinine in around 50% of the patients. Still, close monitoring of these patients is important to ensure a timely treatment to save as much kidney function as possible in the case of a continuous rise in p-creatinine.

The results of this study reflect the everyday clinical reality of patients receiving treatment with ICIs in terms of the risk of developing AKI.

The kidney function in patients with metastatic RCC was generally more severely affected compared to patients with MM in terms of CTCAE grade (Table 1) possibly explained by a higher presence of comorbidities in these patients.

In this study, we chose to define AKI using the KDIGO clinical practice guidelines and to define a case as potential ICI-related AKI if it was diagnosed as such in the hospital records.

The latest ASCO guidelines [6] distinguish between definite, probable, and possible ICI-related nephritis or AKI. The diagnosis is not certain unless a kidney biopsy is performed but is considered probable when a patient has both sustained increases in serum creatinine $\geq$50% on at least two consecutive values or need for RRT and sterile pyuria and/or concomitant or recent extrarenal eosinophilia. In the present study, only two patients out of the total seven patients with potential ICI-related AKI had a level of eosinophils in their blood slightly above the reference interval. Still, the remaining five patients responded to glucocorticoid treatment and had no other suspected cause of AKI than ICI-related AKI. Unfortunately, we only had a kidney biopsy to ensure the correct diagnosis in one of the patients with potential ICI-related AKI.

Seethapathy et al. [7] and Stein et al. [8] found a similar incidence of AKI in 17% of the patients receiving ICIs. Seethapathy et al. included 1016 patients receiving either mono- or combination ICI therapy for a wide range of malignant diseases and Stein et al. included 239 patients treated with either nivolumab or pembrolizumab for advanced melanoma.

In line with both studies, we found prerenal kidney injury to be the most common cause of AKI. However, the true causality often remained unclear. ICI-related AKI can only be established with certainty by kidney biopsy which was often not performed. Especially in patients with RCC, where either a partial or total nephrectomy had been performed, and kidney biopsy was contraindicated. In most cases, treatment with high doses of glucocorticoid was initiated upon admission when ICI-induced acute nephritis was suspected. An improved kidney function after initiation of glucocorticoid

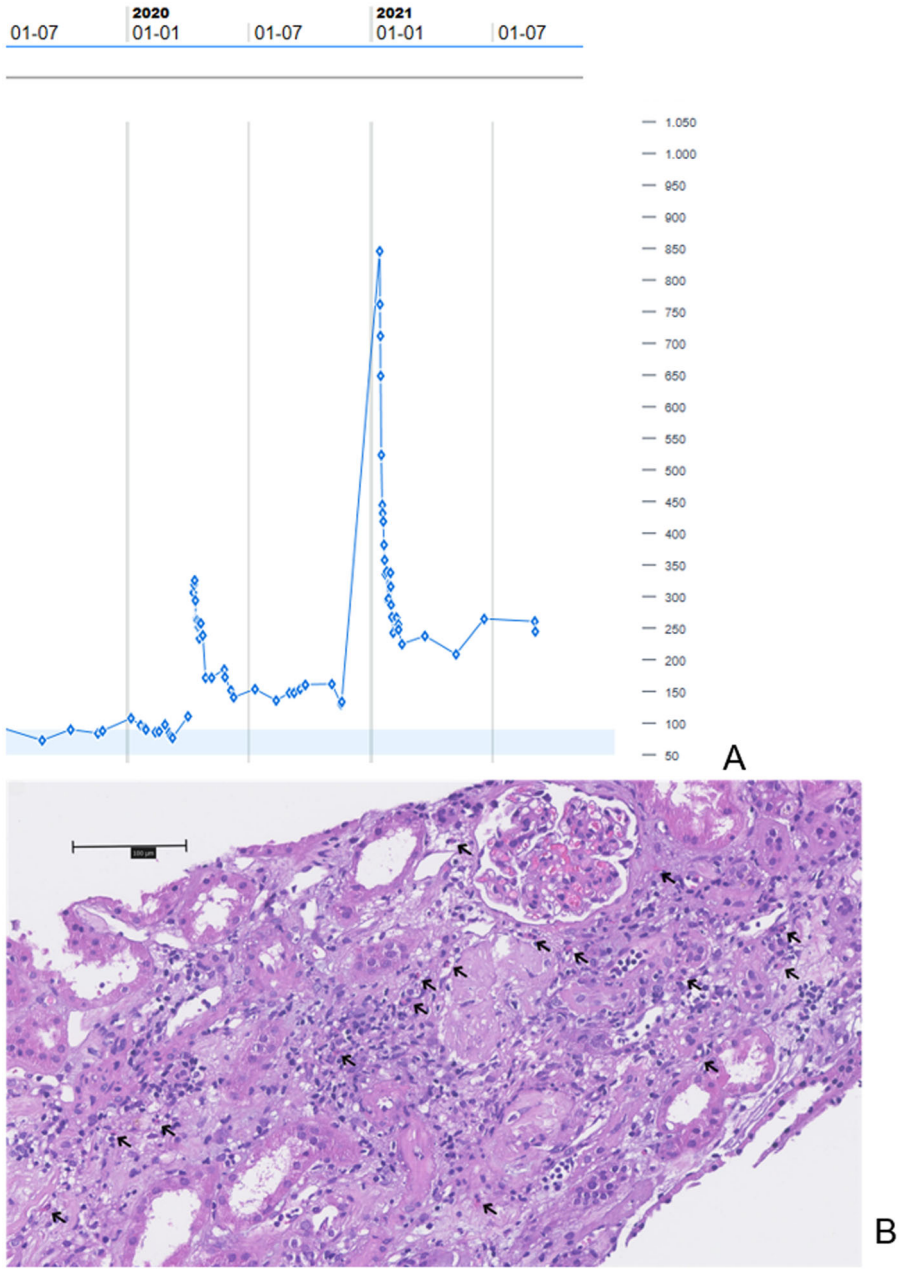

Figure 1. S-creatinine (μmol/L) after treatment with ipilimumab and nivolumab and kidney biopsy showing acute interstitial nephritis. (A) Levels of s-creatinine (μmol/L) after treatment with ipilimumab and nivolumab. AKI occurred 2 and 11 months after receiving treatment with ipilimumab and nivolumab. The AKI responded to treatment with glucocorticoids. S-creatinine was subsequently elevated from the baseline level showing sustained loss of kidney function. (B) The same patient underwent a kidney biopsy showing interstitial nephritis. Renal core needle biopsy with acute interstitial nephritis with interstitial edema and inflammation with scattered eosinophils (arrows) (AIN; hematoxylin and eosin original magnification × 20).

treatment in a patient with no other obvious cause of AKI, ascertained the clinician that it was an ICI-induced AKI. This approach is also in line with the ASCO guidelines which do not routinely recommend renal biopsy but suggests biopsies in cases refractory to glucocorticoids and other immunosuppressant agents [6]. This strategy may increase the risk of missing other causes of AKI and should be accompanied by a thorough examination of other causes of AKI.

PPI was taken at the time of AKI by all patients except one with ICI-related AKI. Only half of the patients with other types of AKI were taking PPI. PPI represents an important cause of AKI worldwide [9] and is a commonly prescribed drug in oncology.

A possible increased risk of nephritis in patients with concomitant use of ICIs and PPI has been suggested by others [8,10], and we strongly support further investigations of this association. The histopathological findings of acute interstitial nephritis represent the primary changes in drug-induced AKI – whether it is related to treatment with PPI or ICIs [11] – which in our view could suggest a lowered threshold for ICI-related AKI in patients treated with PPI.

In the present study, kidney function improved in all patients with ICI-related AKI after receiving treatment with high doses of glucocorticoid. However, the majority had a permanent reduction of kidney function after the episode of ICI-related AKI. The risk of persistently impaired kidney

function after acute interstitial nephritis [11] is not well described. But reduced kidney function following AKI is generally considered more common in older patients and patients with CKD [12] neither of which are uncommon risk factors in oncological patients. One limitation to our study obviously being its relatively small size, this is one important issue that deserves to be studied further in the future.

Conclusion

AKI occurs in around 20% of the patients within 6 months after treatment with combination ICI therapy. Only 17% of these occurrences are considered related to ICI. A thorough work-up for different causes of AKI should always be considered. The use of PPI concurrently with ICIs is likely to increase the risk of AKI.

Disclosure statement

Jesper Andreas Palshof has received grants from Bristol-Myers Squibb for writing information materials to patients about the treatment of renal cell carcinoma. All other authors report no conflicts of interest.

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Data availability statement

According to Danish legislation, data cannot be made freely available without previous permission. The data may be available upon request to the author if allowed by the Danish law on data protection.

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