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Editorial Comment

EDITORIAL COMMENT

Revisiting the role of acute kidney injury in patients on immune checkpoint inhibitors: a good prognosis renal event with a significant impact on survival

Clara García-Carro[1], Kenar D. Jhaveri[2] and Ben Sprangers[3,4]

[1]Nephrology Department, San Carlos Clinical University Hospital, Madrid, Spain, [2]Department of Medicine, Division of Kidney Diseases and Hypertension, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, NY, USA, [3]Department of Medicine, Division of Nephrology, Ziekenhuis Oost-Limburg, Genk, Belgium and [4]Biomedical Research Institute, Department of Immunology and Infection, UHasselt, Diepenbeek, Belgium

Correspondence to: Ben Sprangers; E-mail: ben.sprangers@zol.be

ABSTRACT

In the last decade, immune checkpoint inhibitors (ICI) have become a cornerstone in the treatment of a wide range of malignancies. It is well established that ICI are associated with multiple immune-related adverse events, a spectrum of autoimmune toxicities, that can also affect the kidney. In this issue of *Clinical Kidney Journal*, Kanbay *et al*. report the first meta-analysis and systematic review evaluating the impact of ICI-related acute kidney injury (ICI-AKI) on long-term kidney and patient outcomes (including mortality). The authors report a high incidence of ICI-AKI (mostly mild AKI episodes) with high rates of recovery resulting in a good kidney outcomes. However, the occurrence of ICI-AKI has a significant impact on mortality in ICI-treated patients probably related to temporary or definitive cessation of ICI. Additional studies are needed to establish the safety of ICI re-challenging in patients with ICI-AKI, and to determine the optimal treatment strategy for them.

Keywords: acute kidney injury, immune checkpoint inhibitors, immune-related adverse events, mortality, onconephrology

In the last decade, immune checkpoint inhibitors (ICI) have revolutionized cancer treatment and are now approved in the treatment of numerous malignancies [1, 2]. This group of immunotherapeutic drugs is partially responsible for improving the outcomes of some metastatic tumors [3, 4]. However, ICI are associated with numerous adverse events, termed immune-related adverse events (irAEs), that can also affect the kidney [5]. As ICI use has been expanded, kidney-related toxicities, mainly ICI-related acute kidney injury (ICI-AKI), seem to increase, but reported incidences of ICI-AKI are variable. Moreover, to our knowledge the effect of ICI-AKI on cancer-specific and overall outcome is unknown at this time. The most common histologic lesion that has been associated with ICI-AKI is acute tubulointerstitial nephritis (ATIN), but glomerular lesions (including vasculitis, podocytopathies, C3 GN) have also been reported [6]. The lack of consensus in clinical management of this entity makes ICI-AKI a diagnostic and therapeutic challenge for both oncologists and nephrologists.

In this issue of *Clinical Kidney Journal*, Kanbay *et al*. [7] report the first meta-analysis and systematic review evaluating

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the impact of ICI-AKI on long-term kidney and patient outcomes (including mortality). The meta-analysis by Kanbay *et al.* analyzed seven studies from Europe, North America and Asia totaling 3767 patients with cancer treated with ICI therapy; a total of 895 patients were diagnosed with ICI-AKI. The average age was 61–67 years, and CKD was present in 10%–30% of patients before the onset of AKI. The most common cancers were lung cancer and melanoma, and patients were treated with different ICI namely anti-cytotoxic T lymphocyte-associated protein 4 (anti-CTLA-4), anti-programmed death protein-1 (anti-PD1) and anti-programmed death-ligand 1 (anti-PD-L1), or combinations of these.

One of the most intriguing points of this article is the analysis of ICI-AKI incidences which varied from 17.9% to 76% for AKI stage 1, 7.3% to 57% for AKI stage 3 and 0% to 20% for requirement of kidney replacement therapy. Their results clearly demonstrated that whereas mild AKI is very common, moderate to severe ICI-AKI is less frequent. There is a significant difference in the incidence of AKI in this meta-analysis compared with incidences reported in past studies, e.g. 2%–3% reported such as that of Seethapathy *et al.* [8]. We believe this difference maybe in part ascribed to the inclusion of all types of AKI (prerenal, obstructive, tubular injury) in some studies, rather than true ICI-AKI. Moreover, the higher incidence of mild ICI-AKI might also be the result of the definition of AKI used in different studies and there could be an additional reporting bias.

Although the incidence of ICI-AKI is low, there is a subset of patients who develop severe ICI-AKI and the Onconephrology community should focus on this population as these patients are undoubtedly most likely to experience worse kidney and patient outcomes. The clinical characteristics of ICI-treated patients developing severe AKI and risk factors for severe ICI-AKI are currently not well defined. Risk factors for ICI-AKI in general were described in previous studies included in the present analysis. The key ones were altered baseline kidney function, proton pump inhibitors use, older age, combination of ICI therapies, and the presence of previous and/or concomitant irAEs [9–11]. The creation of an AKI risk stratification tool for ICI treated patients prior ICI treatment initiation could help to prevent the development of ICI-AKI. Could holding proton pump inhibitors at the start of ICI treatment in patients with high risk of AKI help to reduce the incidence of (severe) ICI-AKI? This has not been studied and should be evaluated in future studies. Probably, a nephrologist evaluation in those patients at high risk of AKI before the initiation of ICI would be a reasonable and sound approach. However, referral to nephrology in the setting of ICI-AKI is still a real-world problem, as García-Carro *et al.* recently reported: in a large cohort of 118 patients who developed AKI while on ICI therapy, only 18.6% were referred to Nephrology evaluation [11].

In the meta-analysis of Kanbay *et al.*, rates of fully or partially recovered AKI were difficult to analyze, since available data from every included study had different data sets. Overall, recovery of kidney function was 60% to >80% except for one study, in which the rate of full kidney recovery was only 32%. However, these results suggest that ICI-AKI seems to be a "benign" entity as far as the kidney is concerned, since rates of kidney function recovery are rather high.

Unfortunately, there is currently no consensus regarding the optimal diagnostic strategy and treatment of ICI-treated patients experiencing AKI. Furthermore, recommendations regarding when to perform a kidney biopsy in the setting of ICI-AKI vary widely in currently available guidelines from different oncologic scientific organizations including the American Society of Clinical Oncology, the National Comprehensive Cancer Network, the Society for Immunotherapy of Cancer and the European Society of Medical Oncology. In our opinion, a kidney biopsy is central in order to make a correct diagnosis and avoid unnecessary exposure to steroids (or other immunosuppressive drugs), and the cessation of ICI treatment possibly results in suboptimal cancer outcomes [12]. We recommend a kidney biopsy in ICI-treated patients who develop KDIGO stage 2 or 3 AKI and persistent or progressive KDIGO stage 1 AKI unless there is a clear alternative etiology for the AKI or an absolute contraindication to perform a kidney biopsy [12].

Data regarding the management of ICI-AKI are also scarce. We recommend to hold ICI in persistent or progressive stage 1 AKI and in stage 2 or 3 AKI. We also recommend to start corticosteroids when ICI are considered to be the cause of AKI, or when extra-renal irAEs are present that require steroid treatment [12]. The initiation of corticosteroids does not preclude a kidney biopsy, but initiation of corticosteroids should not be delayed as early initiation has been associated with improved kidney outcomes [12]. In the study of Gupta *et al.*, renal recovery occurred in 64.3% of patients at a median of 7 weeks after the diagnosis of ICI-AKI. Corticosteroid treatment initiated within 14 days after the diagnosis of ICI-AKI was associated with better renal outcomes [13]. To date, there are few data available to guide clinicians in choosing the duration of corticosteroids for ICI-AKI, and consequently treatment duration varies widely in clinical practice. Recently, a multicenter study was conducted with the aim to determine whether a shorter duration of corticosteroids was equally efficacious and safe as compared with a longer duration [14]. The authors analyzed data from 165 patients with ICI-AKI treated with corticosteroids, and concluded that a shorter duration of corticosteroids (28 days or less) may be safe, since they found no difference in the risk of recurrent ICI-AKI or death among patients who received shorter versus longer durations of corticosteroid treatment [14]. However, randomized clinical trials are urgently needed to investigate the indication, dosage and duration of corticosteroids on renal, cancer-specific and overall outcomes in patients with ICI-AKI.

The most relevant result of the analysis by Kanbay *et al.* is the mortality data. It is interesting to note that the mean follow-up in the included studies is only 25–37 weeks, and rates of total mortality are as high as 46%–72%. Despite the discrepancies that exist among the seven studies included in the current meta-analysis, presence and severity of AKI have an impact on all-cause mortality. The risk of death was higher in patients who developed AKI than in those who did not [hazard ratio (HR) 1.42, 95% confidence interval (CI) 1.05 to 1.92, $P = .02$; heterogeneity $\chi^2 = 11.68$, $I^2 = 66\%$, $P = .02$]. Moreover, there was also a trend towards a better survival in those with mild AKI when compared with more severe AKI (HR 1.35, 95% CI 0.99 to 1.83, $P = .05$; heterogeneity $\chi^2 = 0.11$, $I^2 = 0\%$, $P = .74$). Finally, those patients who did not recover kidney function after AKI had also an increased risk of mortality (HR 2.93, 95% CI 1.41.99 to 6.08, $P = .004$; heterogeneity $\chi^2 = 0.53$, $I^2 = 0\%$, $P = .47$).

This high impact of ICI-AKI on mortality is surprising because, as mentioned before, ICI-AKI is often mild with high rates of kidney recovery suggesting a good response to initiated treatments. What is the reason why ICI-treated patients who develop AKI are at higher risk of death than those who do not if AKI seems to be a "benign" entity? Maybe the key point is that in patients with ICI-AKI, ICI are withdrawn forever or, at least, for significant periods of time. Unfortunately, data about ICI withdrawal are not available in the analysis of Kanbay *et al.*, but it is known that stopping the culprit drug is the first step

in the management of patients with ICI-AKI. Knowing that ICI have modified cancer outcomes and clearly improved global outcomes in some malignancies, it seems to be reasonable that ICI withdrawal results in cancer progression and, consequently, increased mortality. However, definite withdrawal of ICI in patients who develop ICI-AKI is not supported by the available data. In the study by Gupta *et al.*, ICI re-challenge was performed in 121 patients with ICI-AKI and recurrent ICI-AKI only developed in 20 patients [13]. Therefore, it is recommended that ICI re-challenge is done in all ICI-AKI patients who have a complete kidney recovery and should be considered in ICI-AKI patients with a partial or no renal recovery after careful assessment of the risk/benefit ratio [12]. In our opinion, future research in ICI-AKI should address the question of when it is safe to re-challenge ICI with the lowest impact on kidney and cancer outcomes. Probably, in some cases, nephrologists should accept some grade of "controlled" kidney damage and kidney function decline to allow the continuation of ICI. As mentioned in the current article, randomized studies investigating the incidence of AKI in cancer patients receiving ICI along with therapeutic alternatives and the effect of AKI on clinical prognosis are needed for the better understanding of this issue and to improve its management.

In conclusion, the paper of Kanbay *et al.* provides a greater understanding of the state of the art of literature about ICI-AKI, despite the study's limitations. In this article, reported ICI-AKI incidences are raised, but mainly due to mild AKI episodes, and patients under ICI who develop AKI have a good kidney prognosis, since rates of kidney function recovery are high. However, AKI has a significant impact on mortality in patients treated with ICI probably due to definite cessation of ICI.

CONFLICT OF INTEREST STATEMENT

C.G.-C. and B.S. are members of the *CKJ* Editorial Board.

(See related article by Kanbay et al. The association between acute kidney injury and outcomes in cancer patients receiving immune checkpoint inhibitor therapy: a systematic review and meta-analysis. *Clin Kidney J* (2023) 16: 817–826.)

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