Kidney Injury in Patients Treated with Immune Checkpoint Inhibitors Does Not Meet KDIGO-AKI Criteria

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Key Points
- Kidney injury in patients treated with immune checkpoint inhibitors develops gradually and often does not meet the Kidney Disease Improving Global Outcomes criteria for AKI.
- Proper classification of kidney injury could prevent the development of CKD and improve continued oncologic treatment.

Introduction
Immune checkpoint inhibitors (ICIs) have prolonged overall and progression-free survival in different types of cancer and have become standard therapy for many patients with cancer (1). Unfortunately, the antitumor immune response induced by ICIs can cause specific immune-related adverse events (irAEs) in almost every organ system (2). Renal irAEs occur in 3%–5% of patients with cancer and are often classified as AKI (3–6). However, data on the rate of kidney function decline over time are frequently not provided.

Materials and Methods
We retrospectively collected data from patients who were referred to our department of nephrology because of deterioration of kidney function while being treated with ICIs or a combination of ICIs and chemotherapy. Changes in serum creatinine levels were evaluated from ICI initiation until reaching a serum creatinine level of ≥1.5 times the baseline level. To classify patients by type of kidney injury, we used the Kidney Disease Improving Global Outcomes (KDIGO) guideline definitions for kidney injury, using serum creatinine as a marker of GFR (7), as follows:

- AKI was defined as an increase in serum creatinine to ≥1.5 times the baseline level, which is known or presumed to have occurred within the prior 7 days; or an increase in serum creatinine by ≥26.5 μmol/L within 48 hours; or oliguria (urine volume <0.5 ml/kg per hour for 6 hours).
- Acute kidney disease (AKD) was defined as AKI; or a GFR of <60 ml/min per 1.73 m² for <3 months; or a decrease in GFR by ≥35% or an increase in serum creatinine by ≥50% for <3 months.
- CKD was defined as a GFR of <60 ml/min per 1.73 m² for ≥3 months.

Due to the routine clinical practice of oncologic care in our hospital, the interval of serum creatinine measurements frequently exceeded 7 days, which made it impossible to use the KDIGO criteria to classify patients as having AKI. Therefore, we formulated an additional definition:

- Possible AKI was defined as an increase in serum creatinine to ≥1.5 times the baseline level, with an increase in serum creatinine of ≥50% between two consecutive samples, with a sample interval >7 days and <3 months.

Baseline creatinine was defined as the mean of all serum creatinine measurements in the 6 months before ICI initiation. If no serum creatinine measurements before ICI initiation were available, serum creatinine at ICI initiation was used as the baseline level. The date of the first ICI administration was defined as time zero.

When serum creatinine had increased to ≥1.5 times baseline, kidney function deterioration was determined by the percentage increase in serum creatinine between this most recent serum creatinine and the previous serum creatinine measurement. When serum creatinine increased by ≥50% between these two consecutive samples, kidney injury was classified as possible AKI. Additionally, the time interval between the last normal serum creatinine measurement and serum creatinine at 1.5 times the baseline level was determined. The last normal serum creatinine measurement was defined as the last value of serum creatinine that deviated <10% from baseline serum creatinine. If serum creatinine reached ≥1.5 times baseline within a time interval of 3 months, kidney injury was classified...
Table 1. Patient characteristics

| Patient | Age, yr | Sex | Type of Cancer | Immune Checkpoint Inhibitor | Immune Checkpoint Inhibitor, n | Concurrent Chemotherapy | Type of Chemotherapy | Chemotherapy, n | Proton Pump Inhibitor | Nonsteroidal Anti-Inflammatory Drugs | Antibiotics | Kidney Biopsy |
|---------|---------|-----|----------------|----------------------------|------------------------------|-------------------------|----------------------|------------------|------------------|-------------------------------------|-------------|--------------|
| 1       | 73      | M   | Merkel cell carcinoma | Avelumab | 7 | No | — | — | Yes | Yes | No | No | TIN |
| 2       | 67      | F   | NSCLC          | Pembrolizumab | 4 | Yes | Carboplatin, pemetrexed | 4 | No | No | No | No | TIN |
| 3       | 59      | M   | NSCLC          | Pembrolizumab | 8 | Yes | Carboplatin, pemetrexed | 8 | Yes | No | No | No | TIN |
| 4       | 74      | M   | Melanoma       | Pembrolizumab | 2 | No | — | — | Yes | No | Yes | No | TIN |
| 5       | 61      | M   | NSCLC          | Pembrolizumab | 20 | No | — | — | No | Yes | No | No | TIN |
| 6       | 71      | M   | NSCLC          | Pembrolizumab | 33 | Yes | Carboplatin, pemetrexed | 4 | No | No | No | No | TIN |
| 7       | 65      | M   | Collecting duct carcinoma | Pembrolizumab | 1 | Yes | Gemcitabine, carboplatin | 6 | No | No | No | N/A |
| 8       | 70      | F   | NSCLC          | Pembrolizumab | 4 | Yes | Carboplatin, pemetrexed | 4 | Yes | No | No | No | TIN |
| 9       | 77      | M   | Laryngeal carcinoma | Durvalumab | 6 | No | — | — | Yes | No | No | N/A |
| 10      | 54      | M   | NSCLC          | Pembrolizumab | 7 | Yes | Carboplatin, pemetrexed | 6 | Yes | Yes | No | N/A |
| 11      | 61      | M   | NSCLC          | Pembrolizumab | 7 | Yes | Carboplatin, pemetrexed | 5 | Yes | No | No | N/A |
| 12      | 71      | F   | NSCLC          | Pembrolizumab | 6 | Yes | Carboplatin, pemetrexed | 5 | Yes | No | No | N/A |
| 13      | 53      | M   | NSCLC          | Pembrolizumab | 6 | Yes | Carboplatin, pemetrexed | 6 | Yes | No | No | N/A |
| 14      | 75      | M   | Melanoma       | Nivolumab | 3 | No | — | — | Yes | No | No | N/A |
| 15      | 75      | M   | NSCLC          | Pembrolizumab | 5 | Yes | Carboplatin, pemetrexed | 5 | No | No | No | N/A |
| 16      | 70      | M   | NSCLC          | Pembrolizumab | 3 | Yes | Carboplatin, pemetrexed | 3 | Yes | No | No | ATN |

M, male; F, female; ICI, Immune Checkpoint Inhibitor; TIN, tubulointerstitial nephritis; NSCLC, non–small cell lung carcinoma; N/A, not available; ATN, acute tubular necrosis.

*Refers to the number of ICI administrations until serum creatinine reached 1.5 times the baseline level.

*Refers to the number of chemotherapy administrations until serum creatinine reached 1.5 times the baseline level.

*Chemotherapy was administered in the months before the start of ICI therapy.
as AKD. If the time interval exceeded 3 months, kidney injury was classified as CKD.

Recovery of kidney function was evaluated. Rapid recovery was defined as a ≥50% decrease of the total serum creatinine increase (maximum serum creatinine minus baseline serum creatinine) within 2 weeks. Duration of follow-up was defined as the time from serum creatinine reaching 1.5 times the baseline level until the last follow-up. Complete recovery at last follow-up was defined as a return of serum creatinine to <25% above baseline at last follow-up.

To estimate referral bias, we additionally screened 100 randomly selected patients who received at least three cycles of ICI in 2019 to evaluate whether these patients developed kidney injury (≥50% increase in serum creatinine), which definition of kidney injury (possible AKI, AKD, or CKD) applied to the patients who developed kidney injury, and whether these patients were referred to the department of nephrology.

In accordance with Dutch law, this study was exempted from formal approval by the medical ethics committee due to its retrospective nature. This was confirmed by our hospital’s institutional review board.

**Results**

We evaluated the course of serum creatinine of 16 patients who were referred to our department of nephrology because of suspected ICI-induced AKI. Patient characteristics are presented in Table 1. Patients had a median age of 70.0 years (range 53–77 years) and 81% were men. All patients were treated with ICIs in the context of palliative care. Five patients (31%) had extrarenal irAEs; two patients (13%) had a history of autoimmune disease.

Patients were classified by type of kidney injury. Seven patients (44%; 95% CI, 20% to 70%) could be classified as having possible AKI, whereas five patients (31%; 95% CI, 11% to 59%) met the criteria of AKD. Four patients (25%; 95% CI, 7% to 52%) had a gradual, persistent decline of eGFR and were classified as having CKD.

As illustrated in Figure 1, only four patients (25%; 95% CI, 7% to 52%) had a distinct AKI pattern. The course of serum creatinine of the other three patients with possible AKI (19%; 95% CI, 4% to 46%) followed a pattern more similar to the patients with AKD. Four of the seven patients with possible AKI showed rapid recovery of kidney function and, in three patients, a prerenal component contributed to kidney injury (Table 2). None of the nine patients were classified as having AKD or CKD showed rapid recovery of kidney function, despite treatment. At the last follow-up, only four out of 16 patients (25%; 95% CI, 7% to 52%) had complete recovery of kidney function.

In the 100 randomly selected patients who received ICI in our center in 2019, we noticed that 15 patients (15%; 95% CI, 9% to 24%) had a serum creatinine increase of ≥50%. In three patients (3%; 95% CI, 1% to 9%), a diagnosis of ICI-related kidney injury was made. Two of these patients were referred to the nephrology department and are included in the cohort with referred patients. One patient had a very gradual increase in serum creatinine (from 82 to 155 μmol/L over a period of 6 months). This patient had not yet been referred to the nephrology department. In 12 patients, kidney injury was attributed to the toxicity of chemotherapy or dehydration and (partly) resolved after withdrawal of treatment. An analysis of the course of serum creatinine of these patients revealed that three patients had possible AKI, four met the criteria of AKD, and five had CKD.
Table 2. Kidney function deterioration and recovery

| Patient | Serum Creatinine at Baseline, μmol/L | Serum Creatinine ≥ 1.5× Baseline, μmol/L | Increase in Serum Creatinine at SCr ≥ 1.5× Baseline, % | Sample Interval, wk | Classification of Kidney Injury | Prerenal Component of Kidney Injury | Steroid Treatment | Rapid Recovery | Serum Creatinine Last Follow-Up, μmol/L | Duration of Follow-Up, mo | Recovery Last Follow-Up |
|---------|----------------------------------|------------------------------------------|-----------------------------------------------|-----------------|-------------------------------|--------------------------------|-----------------|---------------|---------------------------------|-----------------|-----------------|
| 1       | 88                              | 145                                      | 18                                            | 2.3             | AKD                           | No                      | Yes             | No            | 116                             | 11.7            | NR              |
| 2       | 70                              | 112                                      | 29                                            | 1.9             | AKD                           | No                      | Yes             | No            | 154                             | 20.7            | NR              |
| 3       | 62                              | 94                                       | 3                                             | 3.0             | CKD                           | No                      | Yes             | No            | 107                             | 19.9            | NR              |
| 4       | 78                              | 329                                      | 243                                           | 7.3             | Possible AKI                  | Yes                     | Yes             | Yes           | 142                             | 3.9             | NR              |
| 5       | 102                             | 456                                      | 256                                           | 6.0             | Possible AKI                  | Yes                     | Yes             | Yes           | 138                             | 19.1            | NR              |
| 6       | 107                             | 160                                      | 4                                             | 2.0             | CKD                           | No                      | Yes             | No            | 180                             | 43.7            | NR              |
| 7       | 111                             | 202                                      | 120                                           | 2.9             | Possible AKI                  | No                      | Yes             | No            | 153                             | 7.2             | NR              |
| 8       | 50                              | 88                                       | 63                                            | 5.4             | Possible AKI                  | No                      | Yes             | No            | 85                              | 10.7            | NR              |
| 9       | 79                              | 134                                      | 60                                            | 4.0             | Possible AKI                  | No                      | Yes             | No            | 96                              | 8.9             | R               |
| 10      | 93                              | 162                                      | 56                                            | 4.3             | Possible AKI                  | Yes                     | Yes             | Yes           | 99                              | 3.3             | R               |
| 11      | 69                              | 114                                      | 31                                            | 6.4             | AKD                           | No                      | Yes             | No            | 133                             | 11.1            | NR              |
| 12      | 86                              | 133                                      | 6                                             | 3.0             | AKD                           | No                      | Yes             | No            | 133                             | 7.3             | NR              |
| 13      | 113                             | 171                                      | 32                                            | 3.1             | AKD                           | No                      | Yes             | No            | 135                             | 0.9             | R               |
| 14      | 92                              | 522                                      | 449                                           | 3.1             | Possible AKI                  | No                      | Yes             | Yes           | 112                             | 21.5            | R               |
| 15      | 87                              | 131                                      | 15                                            | 5.3             | CKD                           | No                      | No              | No            | 140                             | 4.8             | NR              |
| 16      | 86                              | 133                                      | 19                                            | 7.0             | CKD                           | No                      | No              | No            | 143                             | 20              | NR              |

AKD, acute kidney disease; NR, no recovery of kidney function; R, recovery of kidney function.

*Percentage increase in SCr at 1.5 times the baseline level compared with previous serum creatinine measurement.
Discussion

Kidney injury is an important adverse event of treatment with ICIs. Our data indicate that, in most patients, there is a gradual decrease in eGFR, and only four of 16 patients showed kidney function deterioration suspected to be AKI. Thus, ICI-related kidney injury frequently develops in a more subacute pattern.

In literature, ICI-related kidney injury is often characterized as AKI. We performed a structured literature search to evaluate whether the patients reported in literature indeed met the criteria of AKI. We found five studies into ICI-related AKI in the period 2019–2020 that included a minimum of ten patients with ICI-suspected or ICI-related AKI (4,8–11). Together, these studies included a total of 249 patients with ICI-suspected AKI. All studies stated they used KDIGO or Acute Kidney Injury Network criteria to define AKI (7,12). However, although it is evident that the specified cutoff values for serum creatinine increase were used (e.g., 1.5 times [4,8–10] or two times increase [11]), it is not specifically mentioned that the time course was used in the classification of patients. Indeed, Meraz-Muñoz et al. (10) stated in their methods section that they used the KDIGO criteria to classify AKI, but eliminated the “within 7 days” part of the criterion because their mainly outpatient cohort had often not had drawn blood within 7 days before the AKI event. We consider it likely that the same might hold true for the other studies. Therefore, it is unclear whether these patients had true AKI or had a more subacute deterioration of kidney function.

Timely recognition of kidney injury is important to intervene in time and prevent the development of chronic kidney injury. When focusing only on AKI during regular oncology visits, a gradually developing kidney injury might remain unnoticed or is recognized too late. When chronic kidney injury has progressed to a certain extent, this might impair further oncologic treatment options. Furthermore, in the study by Cortazar et al. (11), a lack of recovery of kidney function, defined as serum creatinine more than two times the baseline level, was associated with higher mortality.

Our study has some limitations. We only analyzed patients who were referred to the nephrology department, which might create a selection bias. We performed an additional analysis in which we evaluated the course of serum creatinine in 100 randomly selected patients who received ICIs in our center in 2019. This analysis suggested that referral bias is unlikely because patients who are not referred are even more likely to present with CKD. Moreover, the patients with non-ICI-related kidney injury showed a similar pattern of injury. Another limitation is the low number of events, which led to wide confidence intervals. Large cohorts with properly classified patients are needed to provide meaningful data on the general population.

Kidney injury in patients treated with ICIs often develops gradually and does not meet the definition of AKI. Proper classification and early recognition of patients with kidney injury due to ICIs is needed to improve management and thereby minimize the development of CKD and prevent the limitation of any further oncologic treatment.

Disclosures

B. Piet reports serving as a member of the American Association for Cancer Research (AACR), a member of the American Society of Clinical Oncology (ASCO), a member of the Beroepsgelangen committee, a member of the Dutch Society of Medical Oncology (Nederlandse Vereniging voor Medische Oncologie; NVMO) committee of Off-label indications for Oncological Therapies (CIE-OOM: Offlabelindicaties Ontologische Middelen), a member of the European Society for Medical Oncology (ESMO), and a committee member of the oncology section of the Dutch Society of Pulmonology and Tuberculosis (Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (NVALT); receiving research funding from Amgen, AstraZeneca, Bristol-Myers Squibb, Janssen, Mirati, and Novartis; receiving honoraria from AstraZeneca, Janssen, and Pfizer (for speaker honoraria; no personal honoraria, all paid to the department); and serving as a scientific advisor for, or member of, Bristol-Myers Squibb, Janssen, MSD, Pfizer, and Takeda (no personal honoraria, all paid to the department). J.F.M. Wetzels reports receiving research funding from Alexion and Chemocentryx; serving as a scientific advisor for, or member of, Kidney International; serving on a speakers bureau for Novartis; having consultancy agreements with Novartis and Trave; receiving honoraria from Trave and UpToDate; and serving as an advisor for a patient organization in The Netherlands. All remaining authors have nothing to disclose.

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Author Contributions

M.F.A. Verploen and J.F.M. Wetzels conceptualized the study, wrote the original draft, and were responsible for formal analysis, investigation, and methodology; J.F.M. Wetzels provided supervision; and all authors reviewed and edited the manuscript.

Data Sharing Statement

All data is included in the manuscript and or supporting information.

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