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ORIGINAL ARTICLE

Renal Toxicity From Pemetrexed and Pembrolizumab in the Era of Combination Therapy in Patients With Metastatic Nonsquamous Cell NSCLC

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Received 4 February 2020; revised 12 April 2020; accepted 13 April 2020
Available online - 30 April 2020

ABSTRACT

The combination of chemotherapy and immune checkpoint inhibition (ICI) therapy is the current standard of care for most patients who are fit to undergo treatment for metastatic NSCLC. With this combination, renal toxicity was slightly higher than with chemotherapy alone in initial clinical trials. However, in recent real-world data, loss of kidney function is reported to be more frequent. Both chemotherapy and ICI therapy can induce renal impairment, although the mechanism of renal damage is different. Renal injury from chemotherapy is often ascribed to acute tubular injury and necrosis, whereas the main mechanism of injury caused by ICI therapy is acute tubulointerstitial nephritis. In cases of concomitant use of chemotherapy and ICI therapy, distinguishing the cause of renal failure is a challenge. Discriminating between these two causes is of utmost importance, as it would help assess which drug can be safely continued and which drug must be halted. This review aims to describe the underlying mechanisms of the renal adverse effects caused by chemotherapy and ICI therapy, leading to a suggested diagnostic and treatment algorithm on the basis of clinical, laboratory, radiographic, and pathologic parameters. This algorithm could serve as a supportive tool for clinicians to diagnose the underlying cause of acute kidney injury in patients treated with the combination of chemotherapy and immunotherapy.

Keywords: Renal toxicity; Immunotherapy; Checkpoint inhibitor; Pemetrexed; NSCLC

Introduction

For many years, the first-line treatment for advanced NSCLC was a combination of platinum-based chemotherapy. On the basis of the Keynote-024 study results, in patients with stage IV NSCLC without *EGFR* mutation or *ALK* translocation and programmed death-ligand 1 (PD-L1) expression of greater than or equal to 50%,

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Disclosure: Dr. Dumoulin reports receiving personal and speaker's fee from Merck Sharp & Dohme, Roche Holdings AG, AstraZeneca, Bristol-Myers Squibb, Novartis, and Pfizer outside of the submitted work. Dr. Cornelissen reports receiving personal and speaker's fee from Roche Holdings AG, Pfizer, and Bristol-Myers Squibb; and has served on advisory boards for Merck Sharp & Dohme and Roche Holding AG outside of the submitted work. Dr. Vansteenkiste reports receiving a fee for a lecture conducted for Eli Lilly. Dr. Aerts reports receiving personal fees and nonfinancial support from Merck Sharp & Dohme, Bristol-Myers Squibb, Boehringer-Ingelheim, Amphera, Eli Lilly, Takeda, Bayer, Roche Holdings AG, and AstraZeneca outside of the submitted work; has a patent allogenic tumor cell lysate licensed to Amphera; and has pending patents for combination immunotherapy in cancer and biomarker for immunotherapy. Dr. Gelder reports receiving lecture fees and study grants from Chiesi and Astellas; and consulting fees from Roche Diagnostics, Vitaeris, and Aurinia Pharmaceutical. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2020.04.021

pembrolizumab became the standard first-line therapy because of a significantly longer progression-free and overall survival than with chemotherapy (both $p < 0.001$).[1] Recently, the phase 3 Keynote-189 trial reported that in previously untreated patients with advanced nonsquamous NSCLC without *EGFR* mutation or ALK translocation, the progression-free and overall survival were significantly longer with the addition of pembrolizumab to platinum-pemetrexed chemotherapy than with chemotherapy alone, irrespective of PD-L1 expression of the tumor (both $p < 0.001$).[2] This combination therapy is now considered a standard of care for most patients who are fit to undergo treatment for advanced nonsquamous NSCLC.

One of the major concerns about combination treatment with different antitumor drugs is toxicity, as this may have a major impact on the quality of life and may lead to the withdrawal of effective treatment in patients. Although the overall reported frequency is still low, renal toxicity seems to be more frequent in the setting of the chemotherapeutic agent pemetrexed in combination with the immune checkpoint inhibitor (ICI) pembrolizumab. According to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE version 4.0), in the Keynote-24 trial comparing pembrolizumab with standard chemotherapy in the first-line setting, nephritis grades 3 to 5 were seen in 0.6% of the patients receiving immunotherapy.[1] In addition, increased creatinine was reported in 1.9% of these patients. In the Keynote-189 study, acute kidney injury (AKI), as defined by CTCAE version 4.0, was observed in 5.2% of the patients in the pembrolizumab-combination group compared with only 0.5% in the placebo-combination group. A total of 12.2% of the patients treated with pembrolizumab and carboplatin-pemetrexed revealed all-grade increased blood creatinine, of which 0.7% were grades 3 to 4. Renal adverse events in the pembrolizumab-combination group led to treatment discontinuation in 2% of the patients. Most patients in this trial received chemotherapy with carboplatin as the platinum compound, and only about 25% received the more nephrotoxic cisplatin. Although initial clinical trials reported a low incidence of immunotherapy-related nephrotoxicity, emerging data suggest a higher incidence rate between 13.9% and 29%, especially when chemotherapy and immunotherapy are combined.[3]

Discrepancies between results of clinical trials and real-world data are also present with regard to pemetrexed-induced nephrotoxicity. In the pivotal PARAMOUNT trial (A Phase 3, Double-Blind, Placebo-Controlled Study of Maintenance Pemetrexed plus Best Supportive Care versus Best Supportive Care Immediately Following Induction Treatment with Pemetrexed + Cisplatin for Advanced Non-Squamous Non-Small Cell Lung Cancer), only less than 10% of the patients treated with pemetrexed maintenance therapy experienced renal impairment and less than 5% had to discontinue treatment owing to nephrotoxicity.[4] Several retrospective studies had already described a higher incidence (17%–21%) of renal impairment with pemetrexed.[5,6] In this prospective cohort study by our group, frequencies of approximately 30% for acute kidney disease (AKD) and up to 20% for treatment discontinuation were reported during pemetrexed maintenance treatment.[7]

As platinum, pemetrexed, and pembrolizumab are now often combined, it becomes a challenge to distinguish between chemotherapy- and pembrolizumab-induced renal adverse events. However, discriminating between these causes is of utmost importance as misdiagnosis of the causative agent may lead to inappropriate interventions, which potentially may cause further deterioration of renal toxicity, interruption or even cessation of an effective treatment. This review aims to describe the mechanisms of the renal side effects caused by the frequently used combination of platinum, pemetrexed, and pembrolizumab, leading to a suggested diagnostic and treatment algorithm. Other oncological therapeutic agents will not be covered in this article.

Definition of Renal Toxicity

Estimations of the frequency of kidney injuries in clinical studies depend on how kidney injury has been defined. In the field of oncology, (renal) adverse events are reported according to the descriptive terminologies of CTCAE providing a grading (severity) scale for each adverse event (Table 1).[8] In CTCAE version 4.0, an important adjustment has been made that takes into account the absolute increase of creatinine and its relative increase from baseline. Notably, in the newest version (version 5.0), the lower grades (1/2) of AKI are not anymore defined and severe AKI (grade >3) is only based on the need for hospitalization or dialysis and not on measured kidney function. The Acute Kidney Injury Working Group of Kidney Disease: Improving Global Outcomes (KDIGO) proposed the most frequently used definitions of kidney disease nowadays and they divided renal injury into three categories on the basis of the duration of renal function deterioration: AKI, AKD, and chronic kidney disease (CKD) (Table 1).[9] All individuals, including the elderly, with a glomerular filtration rate (GFR) less than 60 mL/min are considered to have CKD.[9] Although some decline of GFR is expected with age, most healthy older individuals do not necessarily have a decreased GFR.[9] Moreover, among older individuals,

Table 1. Definitions and Classifications of Kidney Injury According to CTCAE and KDIGO

CTCAE						
Version 3.0	Grade 1	Grade 2	Grade 3	Grade 4		
Creatinine	>ULN-1.5 × ULN	>1.5-3.0 × ULN	>3.0-6.0 × ULN	>6.0 × ULN		
GFR	<75%-50% LLN	<50%-25% LLN	<25% LLN, chronic dialysis not indicated	Chronic dialysis or renal transplant indicated		
Version 4.03						
AKI	Creatinine level increase of >0.3 mg/dL (26.5 μmol/liter); creatinine 1.5-2.0 × above baseline	Creatinine 2-3 × above baseline	Creatinine >3 × baseline or >4.0 mg/dL (354 μmol/liter); hospitalization indicated	Life-threatening consequences; dialysis indicated		
Version 5.0						
AKI[a]	—	—	Hospitalization indicated	Life-threatening consequences; dialysis indicated		
KDIGO						
AKI	Increase in serum creatinine by 50% within 7 d or Increase in serum creatinine by 0.3 mg/dL (26.5 μmol/liter) within 2 d or Oliguria[b]					
	Stage 1		Stage 2		Stage 3	
	Creatinine: 1.5-1.9 × baseline or ≥ 0.3 mg/dL (26.5 μmol/liter)		Creatinine: 2.0-3.0 × baseline		Creatinine: >3.0 × baseline or ≥ 4.0 mg/dL (354 μmol/liter)	
AKD	AKI or GFR < 60 mL/min per 1.73 m^2 for <3 mo or decrease in eGFR by >35% or increase in serum creatinine >50% for <3 mo					
CKD	GFR <60 mL/min per 1.73 m^2 for >3 mo					
	G1 (normal)	G2[c]	G3A	G3B	G4	G5 (renal failure)
	GFR ≥90	GFR 60-89	GFR 45-59	GFR 30-44	GFR 15-29	GFR <15

[a]A disorder characterized by the acute loss of renal function (within 2 weeks).
[b]Oliguria is also used in the staging of AKI, but it is not further discussed here.
[c]GFR 60-89 mL/min is considered to be mildly decreased, but the threshold of GFR <60 mL/min (G3a-G5) is chosen for CKD.
AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; CTCAE, Common Terminology Criteria for Adverse Events; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes; LLN, lower limit of normal; ULN, upper limit of normal.

decreased GFR is associated with an increased risk of mortality and kidney failure.[10] In an earlier study by our group, renal adverse events were graded according to CTCAE 4.03 and CTCAE 3.0 to allow for comparison of data from the registration trial of pemetrexed maintenance treatment.[7] Among patients who developed AKD during maintenance pemetrexed therapy per KDIGO definitions, 77% had all grades of renal adverse events using CTCAE 4.03 but only 54% using CTCAE 3.0. Hence, using CTCAE 3.0, we found that only 16% of the patients experienced renal adverse events in contrast with 30% when using the KDIGO definitions. This study illustrates the probable underestimation of renal toxicity by using CTCAE 3.0 and 4.03 than AKD (KDIGO). By taking into account absolute increases of creatinine and its relative increase from baseline, the results of the updated version CTCAE 4.03 corresponded better with the AKD results.

Mechanisms of Renal Toxicity

Antitumor drugs can cause renal toxicity by different mechanisms. Renal injury owing to chemotherapy is often ascribed to acute tubular injury and necrosis (ATN) whereas the main mechanism of injury owing to immunotherapy is acute tubulointerstitial nephritis (ATIN).[11,12] AKI is associated with immediate- and long-term unfavorable outcomes and the development of CKD.[13] Therefore, it is of utmost importance to rapidly identify the cause and start the appropriate management. Uncovering the underlying mechanisms can be the key to the management of AKI during the combination treatment of chemotherapy and immunotherapy. In the case of ATIN, timely administration of steroids can salvage kidney tissues by reducing the amount of tubulointerstitial fibrosis that may ultimately develop.[14]

Below we discuss several separate chemotherapeutic agents used in the treatment of NSCLC in the Keynote-189 trial, followed by ICI.

Cisplatin

Cisplatin is a platinum compound that is widely used as a cornerstone of chemotherapeutic therapy for many carcinomas, sarcomas, and lymphomas. One of its major adverse events is nephrotoxicity, which is often (partially)

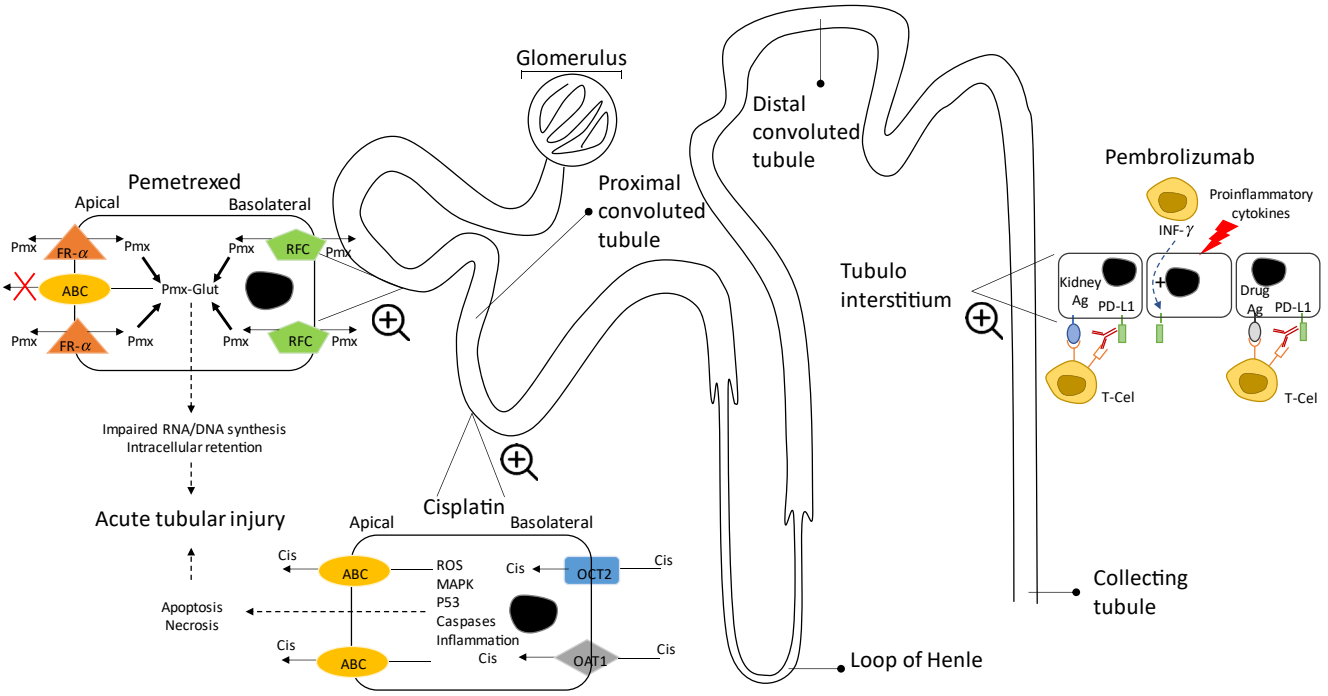

Figure 1. Mechanisms underlying chemotherapy- and immune checkpoint-induced kidney injury. After the entrance of tubular cells, polyglutamation leads to entrapment of pemetrexed in the cell, as these polyglutamates are not substrates for ABC transporters. Impaired RNA and DNA synthesis lead to acute tubular injury. Cisplatin induces multiple intracellular injury pathways, including inflammation, oxidative stress, apoptotic pathways, and DNA damage mediating renal tubular cell injury. Immune activation by checkpoint inhibitors leads to the development of autoimmunity, reactivation of memory T cells previously primed by exogenous drug exposure, and an increase in proinflammatory cytokines/chemokines in kidney tissue. ABC, adenosine triphosphate-binding cassette transporter; Cis, cisplatin; FR-α, folate receptor alpha; OAT1, organic anion transporter 1; OCT2, organic cation transporter 2; PD-L1, programmed death-ligand 1; Pmx, pemetrexed; Pmx-glut; pemetrexed polyglutamates; RFC, reduced folate carrier.

reversible but may be permanent.[15] Cisplatin is principally excreted by the kidneys and thus, its concentrations in the renal cortex are high compared with plasma and other organs.

A key role in the development of cisplatin-mediated nephrotoxicity might be ascribed to basolateral drug transporters, as the expression of proximal tubule organic cation transporter 2 (OCT2) has been reported to influence intracellular accumulation.[16] After cisplatin enters the tubular cell, multiple intracellular injury pathways, including inflammation, oxidative stress, apoptotic pathways, cytoplasmic organelle dysfunction, and DNA damage can contribute to kidney injury.[17] The renal tubular cell injury ultimately leads to clinical AKI by ATN and apoptosis (Fig. 1). Another usually observed manifestation of nephrotoxicity is hypomagnesemia by decreased renal tubular reabsorption, which occurs in 40% to 100% of patients.[18] Less common manifestations of nephrotoxicity are thrombotic microangiopathy (TMA), Fanconi-like syndrome, distal tubular acidosis, and renal concentrating defect.[17] Despite renoprotective strategies including hydration and diuresis, magnesium supplementation, and mannitol, approximately one-third of patients treated with cisplatin still develop renal impairment after the initial dose. Cisplatin-induced nephrotoxicity is dose-dependent and also increases with recurrent drug administration.[19] In patients with thoracic malignancies (mostly NSCLC), cisplatin-induced AKI was observed in 21% of the patients.[15] In this study by our group, the frequency of AKD accumulated from 20% during cycle 1 to 50% during cycle 4 in patients treated with combined cisplatin-pemetrexed treatment.[7]

Carboplatin

Carboplatin has a lesser nephrotoxic profile than cisplatin, despite the fact that the elimination of carboplatin is primarily renal through glomerular filtration. Its lower nephrotoxic potential can most likely be explained by a lack of cell transport by OCT2, thereby reducing proximal tubular intracellular accumulation. In addition, the chloride at cis-position in cisplatin is replaced by carboxylate in carboplatin, which is thought to further

reduce toxicity.[11] Another explanation for the lower incidence of renal toxicity of carboplatin is the fact that dosing is based on the renal clearance of the patient. Thus, in the case of a declining kidney function, the dose of carboplatin will be adapted, which is not the case with patients treated with cisplatin. Nevertheless, renal adverse events are observed during carboplatin-based chemotherapy with direct tubular injury as the most common primary mechanism, followed by magnesium-wasting. A meta-analysis on the basis of individual patient data from phase II and III trials revealed a significantly higher incidence of grade 3 to 4 nephrotoxicity in patients treated with various combinations of chemotherapy combined with cisplatin compared with carboplatin (1.5% versus 0.5%, $p = 0.018$).[20] In a real-life setting, approximately 20% of the patients having carboplatin-pemetrexed treatment developed AKD.[7]

Pemetrexed

Pemetrexed is an antifolate agent that inhibits multiple enzymes involved in the synthesis of purine and thymidine nucleotides. After cell entrance, pemetrexed undergoes rapid intracellular polyglutamation, resulting in polyglutamates that are more potent inhibitors of the enzymatic processes involved in de novo DNA synthesis. Pemetrexed does not undergo substantial metabolization and the unchanged parent compound is primarily eliminated through the kidneys with 70% to 90% of the administered drug excreted unchanged into urine within 24 hours.[21] Although pemetrexed is often combined with cisplatin or carboplatin, pemetrexed monotherapy can also cause renal failure. Although the pathologic mechanism of pemetrexed-induced renal injury is not fully understood, histopathology in several case reports described distinct patterns of tubular toxicity.[11] Reduced folate carrier is the main entrance transporter of pemetrexed and is expressed on basolateral membranes of kidney tubules, whereas the folate receptor-alfa provides drug uptake at the apical site.[11] Pemetrexed polyglutamation results in prolonged retention of polyglutamates intracellularly, which in turn may lead to further impairment in RNA and DNA synthesis and, ultimately, tubular injury (Fig. 1). The cumulative systemic dose of pemetrexed might play a role in the development of nephrotoxicity.[22] Permanent impairment of the kidney function after discontinuation of the pemetrexed maintenance therapy has been reported.[23]

Immune Checkpoint Inhibitors

ICIs are monoclonal antibodies targeted at a specific receptor, either programmed cell death protein-1 (PD-1) or PD-L1, to counteract the blockade of cytotoxic T cells by PD-L1–up-regulating tumor cells. Using this mechanism, the inhibition of T cells is released and the immune system can then effectively kill the cancer cells. However, PD-L1 is also constitutively expressed in renal cells and is up-regulated by IFN-g.[24] By administrating an anti–PD-1 or anti–PD-L1 antibody, the PD-1 receptor will be blocked causing proliferation of T cells and cytotoxic injury of the kidney. It has been speculated that PD-L1 inhibitors potentially lead to less autoimmune toxicity owing to diminished blockade of the negative inhibitory signal, caused by the persistent interaction between PD-1 and its other ligand PD-L2. A systematic review revealed a similar incidence of adverse events in patients treated with PD-1 and PD-L1 inhibitors.[25] Although renal toxicity was not described separately, there was a trend toward a higher incidence of the overall rate of immune-related adverse events (irAEs) with PD-1 inhibitors but the number of grades greater than or equal to 3 irAEs was comparable.

Thus, kidney injury might be caused by the loss of peripheral tolerance of self-reactive T cells against endogenous kidney antigens, leading to an autoimmune variant of interstitial nephritis.[26] Alternatively, ICI may induce reactivation of drug-specific T cells primed by nephrotoxic drugs (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]).[12] As associations between drug-specific T cells and ATIN have been described, it is plausible that ICI may reactivate these latent drug-specific T cells.[27] Another hypothesis-driven explanation is that the increase of proinflammatory cytokines or chemokines may mediate inflammatory injury in the kidney tissue.[28] In contrast with the pharmacokinetics of previously mentioned chemotherapeutic agents, ICIs are not eliminated by the kidneys but cleared primarily by proteolytic degradation in plasma and peripheral tissues.[29]

Renal parenchymal damage because of ICI can be subdivided into two types: ATIN and more rarely, glomerular diseases.[3] In addition, one case report described TMA as a result of checkpoint inhibition.[30] However, TMA is also associated with malignancies in general, which makes it uncertain if TMA can be caused by checkpoint inhibition.[31] TMA is characterized by hemolytic anemia owing to red blood cell fragmentation, thrombocytopenia owing to platelet consumption, and end-organ damage owing to microvascular thrombi.[32] Drug-induced TMA has also been reported after treatment with a number of chemotherapeutic agents, including gemcitabine and the already mentioned cisplatin.[33] The exact incidence of drug-induced TMA is difficult to estimate because cases are underreported and the clinical presentation is sometimes confused with other causes. The mechanism by which the chemotherapeutic agent induces TMA can either be non–dose-

dependent (immune-related) or more frequently dose-related (toxic).[34] In a patient with severe acute renal failure after treatment with the nivolumab and ipilimumab combination therapy, a combination of acute interstitial nephritis and TMA-like lesions were found in the renal biopsy.[35]

ATIN induced by ICI is caused by the migration of T cells into the kidneys resulting in severe inflammatory cell infiltrates with or without granuloma. This mechanism can occur as early as days after treatment initiation but a considerable delay in the development of AIN is often observed with a median time of 3 months and even as late as 12 months in some cases.[12,36] Immune-mediated kidney involvement is relatively rare compared with other organs such as the skin, gastrointestinal tract, endocrine glands, and liver; however, when ICI causes nephrotoxicity, it can be severe and treatment must be initiated quickly. Timely administration of steroids can salvage kidney tissues by reducing the amount of tubulointerstitial fibrosis that may ultimately develop.[14]

Evaluation and Management of Acute Kidney Injury

As described above, renal impairment during treatment with chemotherapy and ICI is common but their pathophysiologic mechanisms are different. The presence of CKD (estimated GFR [eGFR] <60 mL/min) before treatment is a known risk factor for AKI. Baseline renal function should be measured before the start of platinum-pemetrexed treatment and immunotherapy as even mildly decreased renal function (eGFR 60–90 mL/min) can predispose the kidneys to chemotherapy-induced nephrotoxicity.[7,37] In addition to baseline values of creatinine and eGFR, monitoring these parameters during treatment before each (next) administration is needed. Some important pitfalls with regard to measuring renal function must be addressed. First, eGFR is only reliable when plasma creatinine is in steady state, which is not the case in AKI. Therefore, KDIGO states that only an absolute or relative change of creatinine within 48 hours and 7 days, respectively (or loss of urine output), can be used for the diagnosis of AKI (Table 1). The AKD definition takes into account changes in both creatinine and eGFR. In clinical practice, using the AKD definition is more convenient, as it allows for comparison between these values with a time interval up until 3 months. Second, eGFR is dependent on creatinine values. In patients with advanced age, muscle wasting, and poor nutritional status, the use of eGFR may lead to an overestimation of actual renal function.

Before starting chemotherapy in combination with ICI, withdrawal of potential nephrotoxic comedication should be considered. The use of high-dose NSAIDs is (relatively) contraindicated in the days before and after pemetrexed administration and contraindicated in patients with impaired renal function at baseline (Food and Drug Administration–labeled pemetrexed). Besides NSAIDs, interruption of the use of diuretics, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers should be considered, as different studies have revealed an association between nephrotoxicity and the use of these agents during platinum chemotherapy.[38,39] Among patients treated with ICI, 60% were taking drugs known to potentially cause ATIN[40]; thus, discontinuation of these drugs should be considered.

A diagnostic algorithm for AKI during the treatment of chemotherapy in combination with immunotherapy has been developed on the basis of clinical, laboratory, radiographic, and pathologic parameters (Fig. 2).

Clinical Evaluation

When AKI is observed during treatment, it is important to critically evaluate again whether all potential nephrotoxic medication has been withdrawn, if possible. Another mechanism that may contribute to renal failure in patients treated with systemic therapy for lung cancer is intravenous contrast administration during imaging procedures. These agents cause contrast-induced acute kidney injury by direct and indirect nephrotoxic effects.[41] Patients treated with chemotherapy and immunotherapy are frequently exposed to contrast agents because they undergo follow-up computed tomography (CT) scans regularly to evaluate response to the treatment. The KDIGO working group defined contrast-induced AKI (definition in Table 1) as AKI after exposure to a contrast medium. Preexisting CKD is the strongest independent risk factor for contrast-induced acute kidney injury.[41] For this reason, the use of intravenous contrast must be carefully considered in each patient, especially in patients with preexisting kidney disease. Although increments of plasma creatinine levels meeting the AKI criteria are not uncommon, the incidence of severe AKI owing to contrast-enhanced CT is low with a rate of 0.3% postprocedure dialysis.[42]

Therefore, in the context of the frequently detected decreasing renal function in patients undergoing systemic treatment for lung cancer, the risk of using intravenous contrast should be carefully weighed against the benefit and should not be a routine procedure when a CT scan is ordered.

Symptoms may be observed with ATIN, such as generalized malaise, fatigue, weakness, fever, and anorexia. It is impossible to distinguish the cause of these nonspecific symptoms in the presence of malignant disease. Interestingly, in 60% of patients in this case series

reporting on clinical features of immunotherapy-induced AKI, at least one extrarenal irAE was documented before or concurrently with AKI onset.[37] In addition, the time of onset of AKI seems to be delayed with a median of 91 days (interquartile range 60–183 d) and patients could still develop ATIN 2 months after treatment discontinuation.[12] Thus, concomitant extrarenal irAEs at the time of AKI may raise the suspicion of immunotherapy-related renal toxicity. The timing of AKI is unlikely to help distinguish between immunotherapy- or chemotherapy-related renal toxicity during combination treatment, except for patients who have a very rapid onset of renal impairment after initiation of the treatment, which is suggestive of chemotherapy-related toxicity.

Blood Testing

None of the blood tests is helpful in pointing the differential diagnosis of AKI toward ATIN. Serum eosinophils may be moderately or highly elevated (up to 50%–75% of the total white blood cell count).[43] However, in a case series on renal failure, only one of the 12 patients (8.3%) treated with ICI had eosinophilia.[12] Eosinophilia is also associated with NSCLC and the use of immunotherapy and therefore is not a specific marker.[44]

Blood tests in combination with urine chemistry studies may be helpful in distinguishing prerenal versus renal injury from ATN. Fractional excretion of sodium (FeNa) and urea (FeUrea) can be calculated and are measures of tubular resorption of sodium and urea, respectively. A FeNa of less than 1% in patients depleted with volume is suggestive of prerenal acute kidney injury; however, its value is unreliable during the use of diuretics.[45] In such cases, FeUrea is more accurate, with the FeUrea usually less than 35% in prerenal disease.[46] Patients with ATIN may have FeNa values of less than 1% or greater than 1%; therefore, FeNa is useless for diagnosing ATIN.[45] FeUrea has not been properly evaluated in this population.

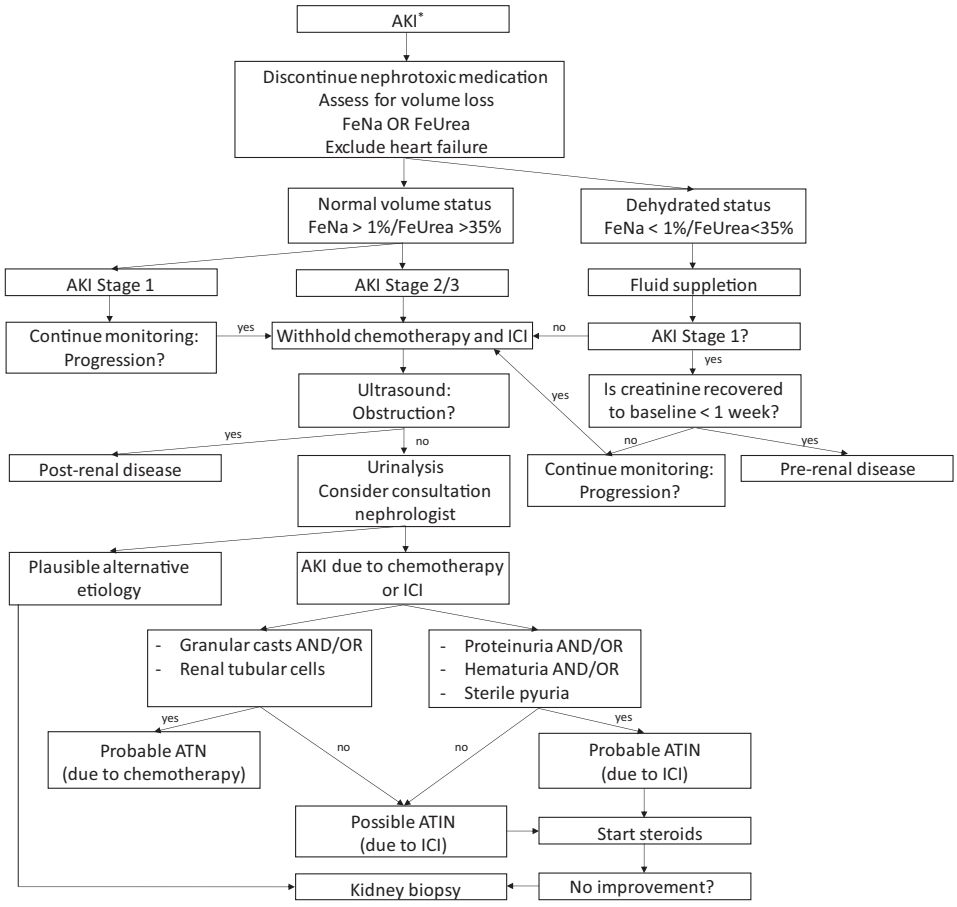

Figure 2. Diagnostic and treatment algorithm for renal injury during combination chemotherapy/immunotherapy. *AKI is defined and staged according to the KDIGO guideline[9], but decreases in eGFR and a longer time interval (<3 mo) for renal injury to develop on the basis of the AKD definition should be taken into account. AKI, acute kidney injury; ATIN, acute tubulointerstitial nephritis; ATN, acute tubular necrosis; eGFR, estimated glomerular filtration rate; FeNa, fractional excretion of sodium; eUrea, fractional excretion of urea; KDIGO, Kidney Disease Improving Global Outcomes; ICI, immune checkpoint inhibitor.

As mentioned above, it is important to take into account the kidney function before treatment, as a decreased creatinine clearance (CrCl) at baseline may be predictive of sensitivity to kidney dysfunction during treatment. In our previous study, we also established that a decline in renal function during treatment is predictive for developing renal failure.[7] In addition, the trend of renal function during treatment should be noted. Although values may still be within a normal range, a decreasing renal function during induction treatment may predict the occurrence of AKI during maintenance treatment.[7]

Urinalysis

Urinalysis is a simple test but is the most important noninvasive test in the general workup of AKI (Table 2). In ATIN, sterile pyuria is present in most cases, and microscopic hematuria without casts can be seen, suggesting nonglomerular disease. Proteinuria is mild, generally revealing protein concentrations less than 2 g/d. White blood cell casts may be observed, although sensitivity is low.[47] In contrast, ATN is characterized by the presence of (deeply-pigmented) granular and/or renal tubular epithelial cell casts with or without free renal tubular epithelial cells.[48]

PD-1–related ATIN seems to present similarly to other causes of ATIN, with evidence of pyuria and subnephrotic-range proteinuria in 60% and 50% of the patients, respectively.[12] Red blood cells were also detected in approximately 60% of the patients. Urinary cytokine IL-9 and tumor necrosis factor-α effectively distinguished ATIN from other renal lesions in patients treated with ICI, but these biomarkers still need validation.[49]

Imaging

If prerenal disease is excluded or severe AKI is present, an ultrasound should be performed to rule out postrenal disease caused by urinary tract obstruction. A CT may be performed when hydronephrosis or urinary tract obstruction cannot be reliably excluded by ultrasound. Kidney imaging with gallium-67 scintigraphy has been proposed in the evaluation of ATIN, as positive enhancement is seen if the administered gallium-67 binds to lactoferrin, which is released by leukocytes within the kidney interstitium. However, sensitivity (58%–100%) revealed a large variation and specificity (50%–60%) is low.[50] The role of imaging during the workup of AKI in chemotherapy and immunotherapy combination is limited to excluding postrenal disease. However, when imaging procedures are requested, the use of intravenous contrast must be carefully considered to prevent further decrease in kidney function.

Renal Biopsy

The regular procedure for the distinction between chemotherapy- or immunotherapy-induced renal toxicity is a renal biopsy. Renal toxicity caused by chemotherapy reveals ATN, whereas renal toxicity as a consequence of immunotherapy reveals ATIN (Fig. 3). ATIN is characterized by marked mononuclear cell infiltration and a variable number of lymphoid follicles and tubulitis. There is a strong infiltration of mainly $CD3^+$ T cells, many of which are $CD4^+$ T helper cells with a mild infiltrate of $CD8^+$ cytotoxic T cells and $CD20^+$ B-lymphocytes (Fig. 3B–D).[12] $CD68^+$ and $CD163^+$ macrophages are also seen, together with $CD1c^+$ dendritic cells. The more uncommon mechanisms of immunotherapy-induced renal disease have previously been published as case reports and these include TMA, minimal change disease, immune complex glomerulonephritis, and drug-induced lupus nephritis.[51-53] Although TMA can be diagnosed histomorphologically, minimal change disease can only be diagnosed with confidence using electron microscopy and the latter two require confirmation through the exhibition of the characteristic immunofluorescence staining pattern.

The timing of a kidney biopsy is disputable and often depends on the subjective judgment of the clinician. Empirical treatment with steroids after ruling out prerenal and postrenal causes of renal injury is recommended for most patients. A renal biopsy is indicated directly for patients who are likely to have an alternative cause of renal injuries, such as glomerulonephritis (i.e., not ICI-related), and for patients who do not recover even with high doses of steroids.

Management

In grade 1 AKI, it is recommended to continue ICI and monitor closely; whereas in grade 2 to 4 AKI, discontinuation of treatment should be done with prompt initiation of steroids, while at the same time exploring the exact cause of AKI.[54] In patients with grade 4 AKI, immunotherapy should not be restarted. This review of observational studies revealed that most patients (80%) received corticosteroids and that immunotherapy was discontinued (90%) if ATIN was noted during treatment with ICI; however, the approach with regard to dose and length of corticosteroid treatment was highly variable.[40] Only one-third of these patients had complete recovery of their kidney function and 10% of the patients needed renal replacement therapy. There is a need for better immunopathophysiologic knowledge and biomarkers to develop more personalized therapeutic drug regimens for severe and refractory irAEs.[55]

In the case of severe kidney injury most likely caused by chemotherapy, dose reductions or discontinuation

Table 2. Urinalysis in ATIN and ATN

	ATIN	ATN
WBC	+[a]	0
WBC casts	+	0
RBC	+	0
Protein	+	±
Renal tubular cell casts	±	+
Granular casts	0	+

[a]Eosinophiluria may be present.
ATIN, acute tubulointerstitial nephritis; ATN, acute tubular necrosis; RBC, red blood cell; WBC, white blood cell.

should be considered, although extensive data supporting such recommendations are lacking.[56,57] According to Kintzel et al.,[56] in patients treated with cisplatin, a dose reduction of 25% is suggested for CrCl of 46 to 60 mL/min and a 50% dose reduction for CrCl of 30 to 45 mL/min, whereas Aronoff et al.[57] still recommend cisplatin administration in patients with more severe renal impairment. Substituting cisplatin with carboplatin is a pragmatic approach in most patients with advanced NSCLC. For carboplatin, renal function-based dose adjustments, using the Calvert formula, are recommended, capping the maximum carboplatin dose on the basis of the target area under the curve. In patients treated with pemetrexed, dose adjustment is not necessary for patients with a CrCl greater than or equal to 45 mL/min, and it is not recommended to use the drug in patients with a CrCl less than 45 mL/min, although data about these patients are scarce.[58] Pemetrexed dosing is basal surface area–based; however, increasing evidence suggests that renal function is the main predictor of pemetrexed clearance and, thus, exposure.[59] Therefore, a renal-based dosing may result in more stable exposure and less toxicity. Currently, a phase II study is assessing the feasibility of renal function–based dosing of pemetrexed in patients with impaired renal function and CrCl of less than 45 mL/min (IMPROVE-I, ClinicalTrials.gov Identifier: NCT03656549).

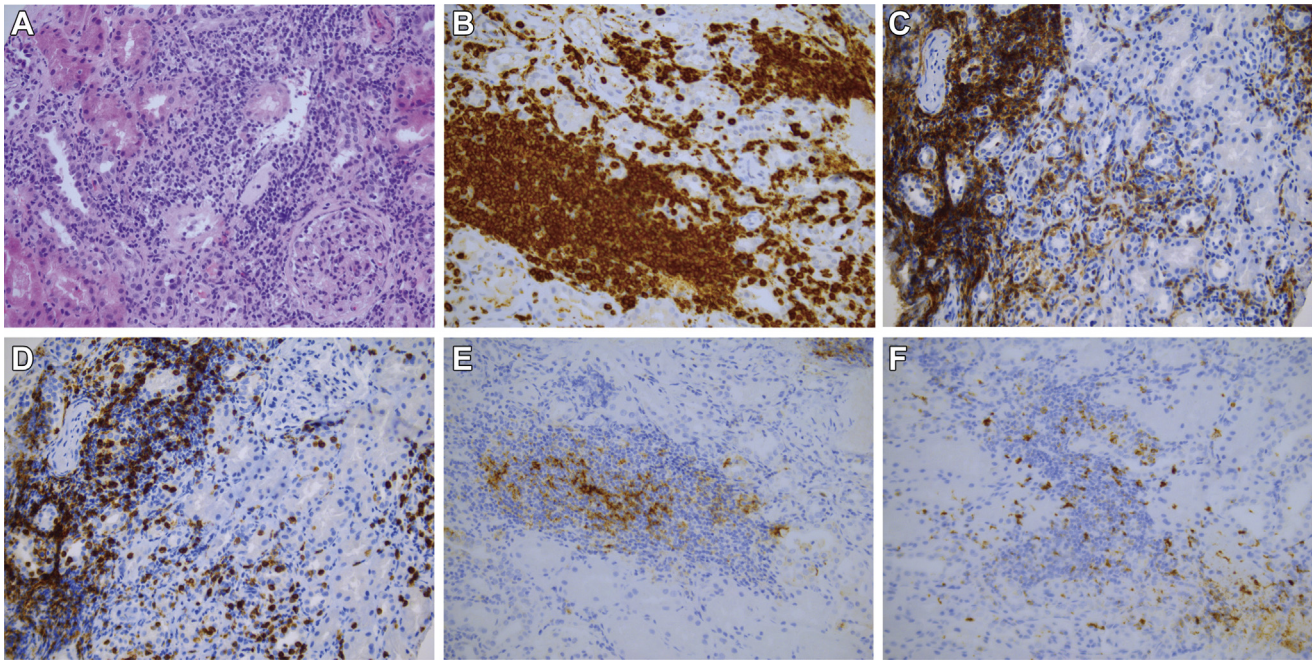

Figure 3. Kidney biopsy with tubulointerstitial nephritis. *(A)* Hematoxylin and eosin stain, revealing extensive immune cell infiltration in the kidney parenchyma, affecting, and displacing tubules but not encroaching on glomeruli (bottom right). *(B)* Immunohistochemical stain for CD3, revealing aggregates of T lymphocytes, and tubulitis. *(C)* CD4 stain, positive in histocytes, and helper T cells in the interstitial stroma but not present in tubules. *(D)* CD8, positive in cytotoxic T cells in the stroma and present in intratubular lymphocytes. *(E)* PD-L1, limited to lymphoid aggregates, likely positive in dendritic/antigen-presenting cells. *(F)* PD-1 stain, positive in lymphocytes, within and outside of aggregates/follicles. PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1.

Discussion

Combination chemotherapy and immunotherapy with PD-1/PD-L1 inhibition improves survival in patients with NSCLC. The hypothesis is that chemotherapy increases the responsiveness to ICI, causing some synergistic effects, with outcomes superior to the administration of both therapies in a sequential way. This also holds true for the maintenance phase, in which it is recommended to continue treatment with pemetrexed in combination with pembrolizumab.

The gain in survival benefit owing to the combination of chemotherapy and immunotherapy probably increases the willingness of patients to undergo the treatment. This will lead to a larger treatment population in clinical practice, including patients who are frail and are more prone to treatment adverse effects. Given the advanced age and the cardiovascular comorbidities often seen in patients with lung cancer, renal side effects are more frequently seen in a general population than reported in clinical trials.[7]

Some important challenges are encountered in clinical practice when dealing with a renal injury during the combination with chemotherapy and ICI treatment. We need to be aware of not only the underestimation of kidney injuries in clinical trials but also of the large variations in incidence that may be reported owing to the use of different definitions. In particular, the latest CTCAE (version 5.0) may falsely report low numbers, as only kidney disease leading to hospitalization will be scored. In addition, rather than using a single eGFR and creatinine measurements alone, we emphasize looking at the trend during the total treatment period. Further complications during maintenance treatment may be predicted not only by the absolute value of the kidney function but also by its decreasing trend during treatment. For this reason, defining (sub)acute renal injury according to the AKD definition seems most appropriate.

Proper diagnosis of the causes of adverse effects in these patients is of utmost importance to preclude the worsening of adverse effects and decrease in the quality of life. The algorithm described in this article may help clinicians diagnose acute kidney injury in patients treated with a combination of chemotherapy and ICI.

Acknowledgments

The authors thank Jente Klok for her assistance in editing the figures.

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