Cancer drugs and acute kidney injury: new therapies and new challenges

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Purpose of review
Cancer therapies continue to evolve at a rapid pace and although novel treatments, including immunotherapies and targeted therapies have allowed for substantial improvements in cancer survival, they carry associated risks of acute kidney injury (AKI). We aim to summarize the existing literature on AKI associated with the spectrum of systemic cancer treatments, including conventional chemotherapies, newer immunotherapies, and the growing number of targeted cancer therapies, which may be associated with both AKI and 'pseudo-AKI'.

Recent findings
Conventional cytotoxic chemotherapies (e.g. cisplatin and other platinum-based agents, methotrexate, pemetrexed, ifosfamide, etc.) with well recognized nephrotoxicities (predominantly tubulointerstitial injury) remain in widespread use. Immunotherapies (e.g., immune checkpoint inhibitors and CAR-T therapies) may be associated with kidney immune-related adverse events, most often acute interstitial nephritis, and rarely, glomerular disease. Recently, multiple targeted cancer therapies have been associated with reduced renal tubular secretion of creatinine, causing elevations in serum creatinine and apparent 'pseudo-AKI'. To complicate matters further, these agents have had biopsy-proven, 'true' kidney injury attributed to them in numerous case reports.

Summary
Clinicians in nephrology and oncology must be aware of the various potential kidney risks with these agents and recognize those with clinically meaningful impact on both cancer and kidney outcomes.

Keywords
acute kidney injury, cancer, chemotherapy, immunotherapy, nephrotoxicity

INTRODUCTION

Patients with cancer are at high risk of both disease-related and iatrogenic causes of acute kidney injury (AKI), including those caused by cancer drugs. Approximately 9–18% of patients initiating systemic therapies for cancer may experience AKI [1,2]. In patients with cancer, AKI and subsequent changes in kidney function may lead to ineligibility for treatments, delays and dose reductions in therapy and exclusions from clinical trials. All of this, in turn, may lead to worse cancer outcomes, including mortality. As such, appropriate prevention, recognition and management of AKI in this population is crucial to patient outcomes. In this review, we aim to summarize the existing literature on AKI associated with the spectrum of systemic cancer treatments, including conventional chemotherapies, newer immunotherapies and the growing number of targeted cancer therapies, which may be associated with both AKI and 'pseudo-AKI'.

CONVENTIONAL CHEMOTHERAPY

Oncology treatment regimens have changed greatly in recent years with the development and increased use of targeted therapies and of immune therapies, but the use of more conventional cytotoxic chemotherapy treatments is still widespread, and in some malignancies, conventional chemotherapy remains at the forefront. We will briefly discuss some of these

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KEY POINTS

- Novel anticancer therapies including immunotherapies and targeted treatments have improved survival outcomes; they also carry the risk of newly recognized forms of AKI (which may involve various compartments of the kidney).
- Conventional cytotoxic chemotherapies remain front-line treatment options for many malignancies and are associated with frequent nephrotoxicity, most commonly tubulointerstitial injury (e.g., cisplatin and other platinum-based agents, methotrexate, pemetrexed, ifosfamide, etc.)
- Immunotherapies (e.g., immune checkpoint inhibitors), may be associated with kidney immune-related adverse events, most often acute interstitial nephritis, and rarely, glomerular disease.
- Multiple targeted cancer therapies have been associated with reduced renal tubular secretion of creatinine, causing elevations in serum creatinine and apparent 'pseudo-AKI' [e.g. anaplastic lymphoma kinase tyrosine kinase inhibitors (TKIs), cyclin-dependent kinase (CDK) 4/6 inhibitors, poly ADP ribose polymerase (PARP) inhibitors, among others].
- Clinicians in nephrology and oncology should recognize various potential kidney lesions with these therapies, and discern those with clinically meaningful impact on kidney and cancer outcomes.

common treatment options and associated kidney toxicities (Fig. 1).

Platinum-based treatments

Platinum-based treatments have antineoplastic properties by inhibiting DNA replication and are still used frequently. These are used as first-line treatments in some malignancies, mainly breast, uterine and ovarian malignancies. These include cisplatin, carboplatin and oxaliplatin with cisplatin having the highest risk for AKI. Past studies have shown that 10–30% of patients treated with cisplatin experience an AKI [3,4] and recent studies have demonstrated that up to 69% of patients treated with high-dose cisplatin have experienced AKI episodes with 17–51% being stage 2 AKI or above [5,6]. The incidence of AKI may increase with more widespread use of advanced markers for AKI such as Kidney injury Molecule 1 (KIM-1), enabling early detection of AKI [7]. Fortunately, there are some data demonstrating that, in cisplatin-associated AKI, the risk of advancing to an eGFR of less than 29 ml/min within 5 years is under 3% [8]. This study also found that, in AKI following cisplatin treatment, the median initial decline in eGFR was of 10 ml/min/1.73 m^2, but importantly, none of these patients were observed to require dialysis. Risk factors for the development of cisplatin-induced AKI

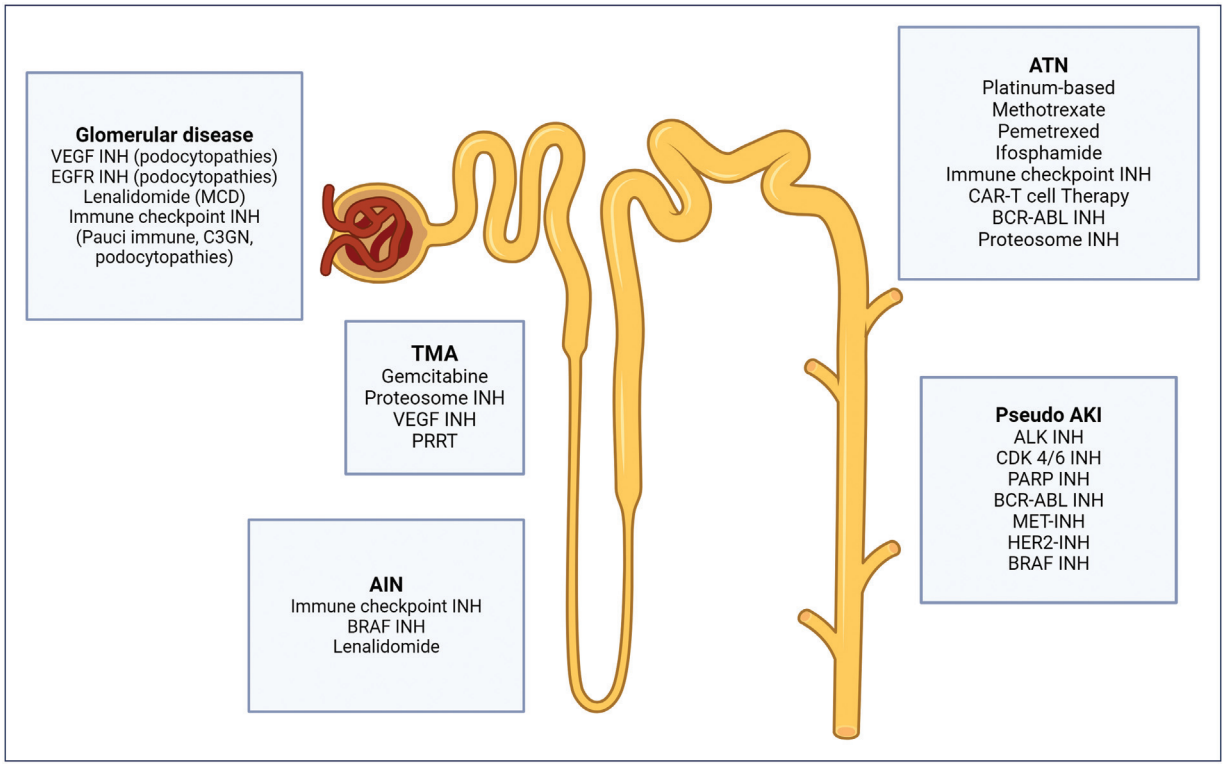

FIGURE 1. Nephrotoxicities and sites of kidney injury associated with systemic cancer therapies.

have been well studied and include age more than 60, hypoalbuminemia, presence of hypertension and cumulative cisplatin dose [9–11] and have incorporated into risk prediction models.

Unbound cisplatin is freely filtered through the glomeruli and then re-absorbed through the proximal tubules, mainly by OCT2 and CTR1 [12,13]. Cisplatin efflux mechanisms include mostly MATE-1 and ABCC2 [14]. Cisplatin nephrotoxicity is caused by inhibition of DNA repair and oxidative stress, a direct result of its antineoplastic properties effecting the renal proximal tubular cells, combined with the fact that the concentration of cisplatin in the kidney is about five times greater than its concentration in other tissues [15,16].

The most effective method for reducing risk for nephrotoxicity has been intravenous fluids subsequent to cisplatin treatment. Different protocols were examined in a systematic review with final recommendations suggesting 2–4 l of isotonic saline over 2–6 h [17]. Other methods of preventing or reducing cisplatin nephrotoxicity have focused on inhibiting cisplatin uptake with drugs such as cimetidine or pantoprazole [18,19], increasing efflux and reducing oxidative stress. Magnesium supplementation has also been shown to reduce cisplatin-related nephrotoxicity, most likely due to OCT2 inhibition, but the desired levels of magnesium have not been determined [20,21]. Recent studies have examined other treatment options (examples include Pim1 proto-oncogene, Vitamin D receptor activation, AZD4538 and Dabrafenib) that have shown some promise in animal models, but none has been shown to be effective in humans [22–25,26▪].

Carboplatin and oxaliplatin are also known to cause nephrotoxicity but with a significantly reduced risk compared to cisplatin (with carboplatin still more frequent than oxaliplatin) [27–30]. These treatments are unfortunately also less effective for certain cancers [31].

Methotrexate

Methotrexate (MTX) inhibits folic acid metabolism and by that damages the cell's ability to divide and produce proteins; this treatment is used mostly in hematological malignancies such as ALL and lymphomas but also sarcomas [32]. MTX is secreted through the kidneys and is known to form crystals that damage the tubular epithelial cells and by that causing acute tubular necrosis (ATN) and AKI [27]. MTX may also cause afferent arteriolar constriction and by that cause glomerular hypoperfusion [33]. MTX toxicity also includes severe cytopenia, mucositis, hepatotoxicity and neuropathy [32,34]. AKI develops in 2–9% of those treated with high dose MTX (HDMTX) [35,36]. Leucovorin is given 24–48 h following HDMTX in order to mitigate its toxicity on noncancer cells [37]. The main preventive measure is by significant hydration and by attempting to alkalinize the urine, as MTX metabolites need an acidic pH to form crystals [32,38]. Since this AKI is mostly asymptomatic, it is critical to monitor urine volume, vitals and MTX serum levels [32,38]. AKI, as well as CKD slows the clearance of MTX and by that increases its exposure and toxicities [39].

MTX is dialyzable but is fat soluble; after initial clearance, there often are rebound episodes and multiple sessions are required [40]. Glucarpidase is a recombinant enzyme that hydrolyzes MTX to inactive metabolites and is considered the treatment of choice for delayed MTX clearance, with expert consensus guidelines advocating for its use in the presence of an AKI in addition to MTX level of more than 50 μmol/l after 24 h or more than 30 μmol/l after 36 h [41▪▪,42]. Unfortunately, this treatment is relatively costly and as such, not accessible everywhere [43].

Pemetrexed

Pemetrexed is currently primarily used in lung cancers and mesothelioma. It is a multitargeted antifolate and by that inhibits cell growth [44]. The incidence of AKI is difficult to assess as pemetrexed is usually given with other agents with nephrotoxic potential, such as platinum-based chemotherapies. Some studies reported an incidence of 6–20% [45,46]. It has been shown that the cumulative dose of pemetrexed is a significant risk factor for AKI, with 10 or more cycles increasing the risk for AKI [47]. Pemetrexed induces different renal diseases, including ATN, interstitial fibrosis, nephrogenic diabetes insipidus and renal tubular acidosis [48–50]. Pemetrexed nephrotoxicity is often irreversible and could lead to chronic kidney damage [51]. Treatment focuses on holding pemetrexed, avoiding other nephrotoxic agents, folic acid supplementation and supportive treatment [52]. Since pemetrexed is secreted by the kidney and could cause life-threatening toxicity, its use is contraindicated for CrCl less than 45 ml/min [53]. Pemetrexed is often given in conjunction with immunotherapy, and AKI in this setting is especially challenging, as it requires distinguishing between these two potential causes and corresponding treatment [54].

Gemcitabine

Gemcitabine is a difluorinated analogue of deoxycytidine, used mostly in combination with platinum-based treatments in several solid organ malignancies. Type I Drug-related thrombotic microangiopathy (TMA), originally described as hemolytic uremic syndrome, or HUS was described with gemcitabine in 1994 during a phase II trial [55];

subsequently in further cohorts, this is mainly presented as hypertension, thrombocytopenia and AKI. This toxicity manifested several months following gemcitabine treatment and, in some cases, after completing treatment [56,57]. One study found that 42% recovered with cessation of treatment and with supportive care [58]. For unresolved cases, treatment with Eculizumab has been effective with one study demonstrating improvement in kidney function in over 80% [57,59–61].

Ifosfamide

Ifosfamide exposure may result in several kidney injuries, including proximal tubular dysfunction, AKI and later CKD [62]. These could result in electrolyte abnormalities such as hypophosphatemia and rickets in children [63]. Treatment is supportive as no established treatment is known. The treatment should be stopped, and kidney function monitored. Prevention of hemorrhagic cystitis is customary with mesna.

IMMUNE CHECKPOINT INHIBITORS

The use of immune checkpoint inhibitors (ICIs) has revolutionized the landscape of cancer therapy since the first drug, ipilimumab, a mAb against cytotoxic T-lymphocyte associated protein-4 (CTLA-4), was first approved in 2011 by the U.S. Food and Drug association (FDA) for the treatment of metastatic melanoma [64]. Since then, six more drugs which target the programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PDL-1) have been approved to be used either in combination with CTLA-4 inhibitor or as monotherapy in up to 17 types of malignancies. By inhibiting either CTLA-4, which is predominantly expressed on T-cells, or PD-1/PDL-1, which is expressed on T cells and tumor/antigen presenting cells respectively, ICIs remove negative feedback and allow T-cell activation and cytotoxic killing of tumor cells. As a result of enhanced T-cell activation, ICIs are associated with a unique spectrum of immune-related adverse events (irAE), with skin, endocrine and gastrointestinal tracts most involved. Overall AKI incidence in patients receiving ICIs has been reported to be in the range of 17% [65]. However, AKI due to kidney irAEs to ICIs is less common, with an estimated incidence of 3–5% [62]. Combination therapy with dual blockade of CTLA-4 and PD-1/PDL1 is associated with higher incidence of AKI, as well as concomitant use of proton pump inhibitor (PPI) [66,67]. Extrarenal irAEs are commonly present at the same time or prior to the onset of AKI [68]. The time of onset of AKI secondary to ICIs is variable, with the median interval at 16 weeks from the initiation of ICIs in a multicenter study [68]. Interestingly, a recent Danish population cohort study found the relative risk between PPI use and development of AKI in patients on ICI is much lower at 1.06 [69], whereas a Taiwanese meta-analysis found the use of PPI is associate with an odds ratio (OR) of 2.42 [95% confidence interval (95% CI) 1.96–2.97] for ICI-related AKI [70▪].

The most common pathological finding in AKI secondary to ICIs is acute tubulointerstitial/interstitial nephritis, accounting for up to 90% of the reported kidney biopsies [64,66,67]. Other biopsy-proven lesions include acute tubular injury/necrosis and glomerular diseases. A systemic review of 45 biopsy proven glomerular disease found the most common glomerular lesions were pauci-immune glomerulonephritis/renal vasculitis (27%), podocytopathies, including minimal change disease and FSGS (24%), and C3GN (11%) [71].

Clinical features of AKI secondary to ICIs may be nonspecific, and include pyuria, hematuria, subnephrotic proteinuria and elevated creatinine. Kidney biopsy remains the gold standard of diagnosis, especially if there is a need to rule out other causes, which may require different treatments, or if AKI is refractory to standard steroid treatment for presumed AIN. We propose a staged approach based on clinical features and other plausible causes as shown in Fig. 2.

PET has been used as an adjuvant diagnostic tool where it is reported to show increased FDG uptake in the kidney cortex [72]. Noninvasive diagnostic tests such as serum and urine biomarkers have been explored in small single-center studies. Most recently, a retrospective review involving 37 patients with ICI-AKI identified serum C-reactive protein (CRP), in conjunction with urine retinol binding protein/urine creatinine ratio (uRBP/Cr), may help to distinguish patients with AKI secondary to ICI from patients with AKI from other causes such as conventional chemotherapies or hemodynamic factors [73]. Other serological markers such as serum sIL-2R level, urinary CXCL-9 and TNF-alpha have been evaluated in small number of patients [74▪,75▪▪].

Corticosteroids are recommended as the first line therapy for moderate to severe stages of ICI-related AKI based on observational studies. Early initiation (within 3 days) of steroid may be associated with improved kidney recovery [68]. The majority of AKI related to ICI are sensitive to steroids with more than 85% patients experience partial or full recovery. Typical regimens include prednisone at 1–2 mg/kg (with maximal dose of 60–80 mg), tapering over a course of 4–6 weeks. Intravenous methylprednisolone(500 mg–1 g/day) for three doses could be considered for severe kidney impairment (e.g., stage 3

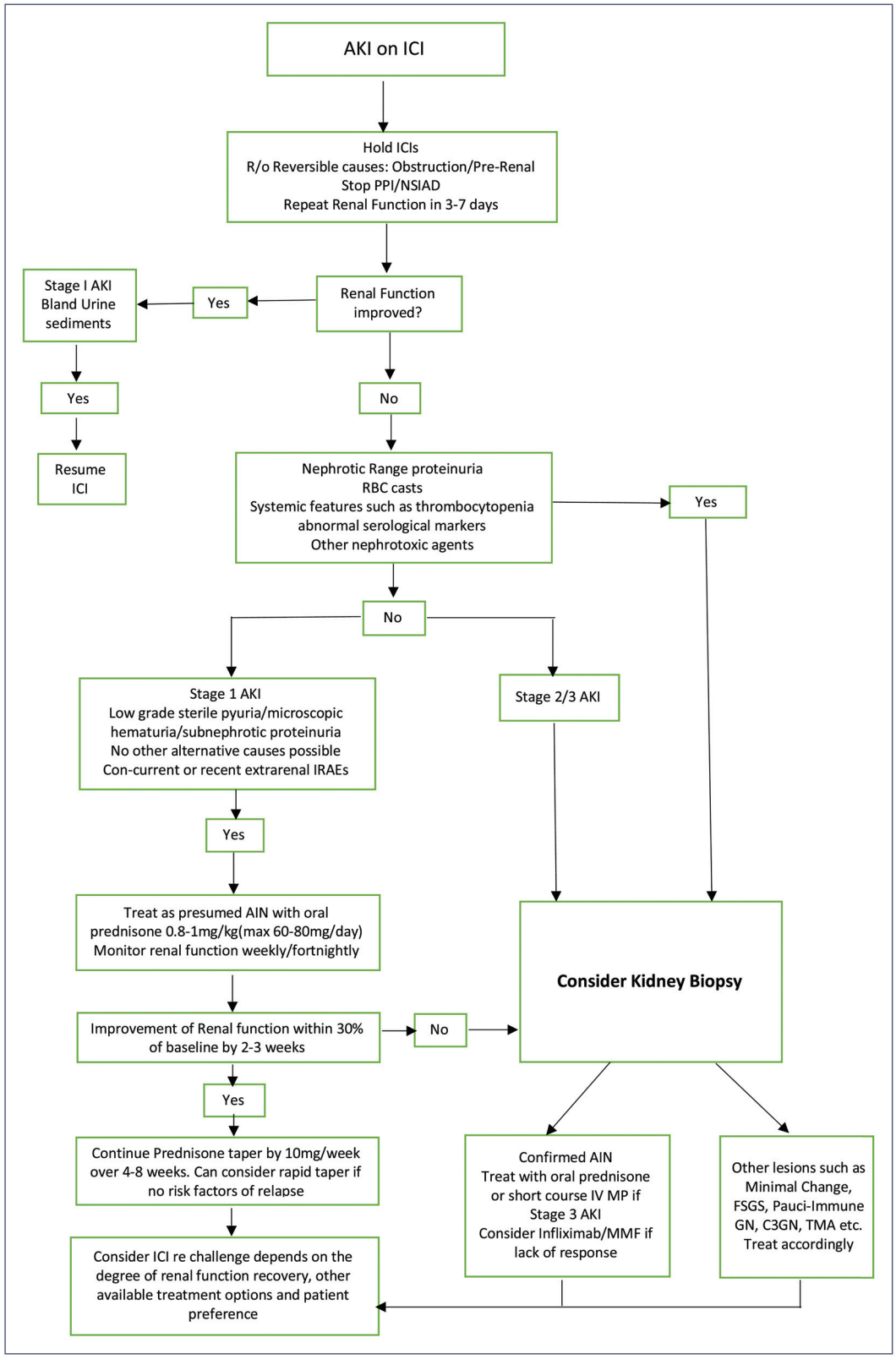

FIGURE 2. Algorithm for the investigation and management of acute kidney injury during immune checkpoint inhibitor treatment.

AKI). There was no particular steroid regimen associated with better renal recovery [67]. Due to the toxicity associated with long-term steroid use, an attempt of rapid steroid tapering has been made. In a single-center study involving 27 patients, equivalent results of renal recovery between rapid taper group ($N = 14$) and standard of care group were found ($N = 13$) [76]. In a large-scale, multicenter cohort study involving 165 patients, patients who received shorter duration of steroid (<28 days) had a similar rate of developing recurrent ICP related AKI or died within 30 days of completing steroid treatment compared to patients who received longer duration of steroids [77]. For patients with AKI secondary to ICIs who are steroid refractory, other immunosuppressive agents have been trialed, including mycophenolate, cyclophosphamide, infliximab, azathioprine and cyclosporine [78], but lack sufficient data to establish preferred second-line therapy. A recent retrospective case series include 10 patients who were treated with infliximab for relapse or refractory ICI-AIN suggested infliximab could be a promising option as a steroid-sparing agent to achieve durable renal recovery [79]. There are also case reports of patients been successfully treated with mycophenolate as a first-line therapy, but data are limited [80].

Patients who developed AKI secondary to ICIs may be challenged again with ICIs based on the degree of kidney recovery, the available cancer treatment options, other extra renal iRAEs, patient comorbidities and preferences. A large multicenter study has showed that the risk of recurrent ICI related AKI is low, between 15 and 25%, and the rate of renal recovery in recurrent AKI is around 60% [68].

In a recent systemic review of 761 patients, ICI-AKI is associated with increased risk of death (hazard ratio 1.42, 95% CI 1.05–1.92, $P = 0.02$), as well as nonrecovery of kidney function [81]. Therefore, early recognition, diagnosis and prompt treatment of AKI secondary to ICI is vital to preserve renal function and allow ongoing immunotherapy treatment.

CHIMERIC ANTIGEN RECEPTOR-T CELL THERAPIES

Chimeric antigen receptor T cell therapy are novel immunotherapies, directing the body's T-cells toward cancerous cells and potentially achieving remission for patients with refractory hematologic malignancies such as multiple myeloma, lymphomas and leukemias. Since these treatments cause an inflammatory response, their side effects include cytokine release syndrome (CRS) and macrophage activation syndrome (MAS). These inflammatory reactions could well lead to AKI due to hemodynamic changes. Another cause for AKI with these treatments is tumor lysis syndrome (TLS). Several studies estimated that AKI occurs in 18–30% of patients treated with CAR-T cell therapies with ATN found in 40% of AKI episodes in one study. In most cases, AKI resolved with supportive therapy [82–84]. Several small studies have also demonstrated that CKD and even ESRD are not limiting factors for CAR-T cell therapy and that treatment results have been similar to patients without CKD or ESKD [85–87].

MOLECULAR TARGETED THERAPY

Targeted therapies include small molecules that target pathways involved in tumor growth, survival and spread. These are either mAb or tyrosine kinase inhibitors targeting single or multiple pathways. These agents are associated with a variety of kidney toxicities and electrolyte imbalances, as well as 'pseudo-AKI' due to inhibition of creatinine transporters on the tubular epithelial cells. Some commonly encountered targeted therapies and cytotoxic agents are discussed in Table 1.

Vascular endothelial growth factor inhibitors

Antiangiogenic agents are associated with dose-dependent hypertension and proteinuria [88]. Bevacizumab has been associated with hypertension in up to 24% of patients in a meta-analysis of over 120 000 patients [89], and Aflibercept has been linked to hypertension in up to 63% of the patients [90]. The incidence of all-grade proteinuria is 10–20% in anti-VEGF treatment [91,92]. Other kidney toxicities include renal limited TMA, podocytopathies, AIN and other glomerulopathies have also been reported in Anti-VEGF agents as well as multi-targeted tyrosine kinase inhibitors (TKIs) such as Sunitinib, Sorafenib, Pazopanib, Pazopanib and Axitinib [93]. Glomerular TMA occurs more commonly in VEGF-Ligand whereas podocytopathies such as MCD/FSGS are more commonly seen in TKIs [93]. TKIs can also cause multiple electrolyte disturbance.

Epidermal growth factor receptor inhibitors

Epidermal growth factor receptor (EGFR) TKIs are used in breast, colon, lung and pancreatic cancers and have been rarely associated with glomerulopathies. Gefitinib has been associated with two cases of minimal change disease [94,95], as well as proliferative IgA crescentic glomerulopathies [96]. Immune-complex glomerulonephritis (GN) has been reported in erlotinib and pantitumumab [97,98]. Osimertinib has been associated with a case of IgA crescentic GN as well [99].

Table 1. Common targeted therapies and known nephrotoxicities

Class	Drug	Kidney toxicity
VEGF Inhibitors [99–104]	mAb against VEGFA Bevacizumab [89] mAb against VEGF2. Ramucirumab Recombinant Fusion protein Aflibercept [90] Multitargeted TKI Sunitinib Sorafenib Axitinib Pazopanib Carbozantinib Lenvatinib Regorabenib Vandetanib Apatinib	Proteinuria [91,92], HTN Renal limited TMA [93] Podocytopathies(MC/FSGS) AIN Electrolytes imbalance
EGFR inhibitors	TKI Erlotinib (1st Gen) Gefitinib (1st Gen) Afatinib (2nd Gen) Brigatinib Icotinib Osimertinib mAb against EGFR Cetuximab Pantitumumab	Crescentic IgA nephropathy [96,99] Immune-Complex GN [97,98] Pauci-Immune crescentic GN MCD/Membranous (Gefinitib) [94,95] Hypomagnesium and other electrolyte imbalance
BRAF + MET inhibitors	BRAF V600E inhibitor [100] Vemurafenib Dabrafenib BRAF+MEK inhibitor [102] Encorafenib+Binimetinib Dabrafenib+Trametinib	Elevated creatinine Acute AIN, ATN Podocytopathy Fanconi syndrome Acute Tubular injury AKI
BCR-ABL inhibitors	1st Gen, target BCR:ABL and KIT Imatinib [93] Target BCR:ABL, PDGFR, KIT. Dasatinib [103–105]	ATN, TLS, Rhabdomyolysis, elevated creatinine (Pseudo AKI), CKD, Fanconi Syndrome Proteinuria, TMA, Rhabdomyolysis
BCL-2 Inhibitors	Venetoclax	TLS
Bruton TKI	Irreversibly inhibits BTK. Ibrutinib	TLS, HTN, AKI
Proteasome inhibitors	Carfilzomib Bortezomib Ixazomib	TMA, TLS, ATN [106–108] (Carfilzomib most common, rare case Bortezomib and Ixazomib)
Immunomodulatory drugs (IMiDs)	Lenalidomide [110–113]	AIN, Fanconi Syndrome, MCD

AIN, Acute interstitial nephritis; AKI, Acute kidney injury; ATN, Acute tubular necrosis; BTK, Bruton's Tyrosine Kinase; CKD, Chronic kidney disease; FSGS, Focal segmental glomerulosclerosis; GN, Glomerulonephritis; HTN, Hypertension; MCD, Minimal Change disease; TKI, Tyrosine Kinase inhibitor; TLS, Tumor lysis syndrome; TMA, Thrombotic microangiopathy.

BRAF and MEK inhibitors

BRAF inhibitors are used in melanoma, and include vemurafenib and dabrafeinib, which have been reported to cause AKI through acute interstitial nephritis or tubular damage [100]. Combination BRAF and MEK inhibitors are associated with lower risk of AKI [101]; however, there have been reports of up to 26% of AKI in the combinations of encorafenib and binimetinib as well as dabrafenib and trametinib [102].

BCR-ABL inhibitors

Imatinib, a first-generation TKI, is used in chronic myelogenous leukemia (CML), gastrointestinal stromal tumors, among others. It targets BCR-ABL, c-KIT and PDGFR, and has been associated with AKI, which includes acute tubular injury, tumor lysis syndrome, rhabdomyolysis, as well as elevated creatinine [93]. Dasatinib is used to treat imatinib-resistant CML and has been reported to cause TMA and proteinuria [103–105].

Proteasome inhibitors

These agents remain the mainstay of multiple myeloma therapy. Carfilzomib has been associated with elevated creatinine in up to 25% of patients, as well as TMA, ATN and tumor lysis syndrome [106–108].

There have been rare case reports of TMA in patients on Bortezomib and Ixazomib as well [109].

Immunomodulatory myeloma drugs

Lenalidomide has been associated with several types of kidney injuries, and include acute interstitial nephritis, minimal change disease and Fanconi syndrome [110–113]. Thalidomide and Pomalidomide are not commonly associated with direct kidney toxicities.

PSEUDO-ACUTE KIDNEY INJURY ASSOCIATED WITH TARGETED THERAPY

It is well recognized that a substantial number of anticancer drugs can cause inhibition of tubular secretion of creatinine, and by doing so, cause an elevation in serum creatinine values without causing kidney damage [114]. These include various targeted therapies that inhibit different transporters such as MATE1, MATE2k and OCT2 [115▪,116]. The common pattern is of an increase in creatinine values days or several weeks following initiation of treatment with creatinine, reaching a plateau on treatment, and reverting to baseline values soon after holding the suspected drug. These creatinine elevations may decrease creatinine-based eGFR values by 2–25% [114]. In suspected cases of pseudo-AKI, noncreatinine-based assessment of GFR should be done. These include serum cystatin C values or measuring GFR by exogenous filtration markers such as ^{51}Cr-EDTA, ^{99m}Tc-DTPA, iothalamate or iohexol. It is important to know these methods and their limitations, especially in cancer patients [117].

It is important to consider the possibility of 'pseudo-AKI' with associated agents, but to also consider other causes of true AKI, and conduct an appropriate work-up, as these drugs are sometimes known to cause true kidney damage. Table 2 lists current treatments known to cause pseudo-AKI and lists other reported kidney injuries related to these drugs.

In case of an increase in creatinine of more than 30% above baseline in a patient treated with pseudo-AKI associated medications, we suggest completing a thorough history with a focus on prerenal causes (i.e., volume depletion), nephrotoxins, ruling out obstructive causes, and completing a serum cystatin C or measured GFR, if possible.

PEPTIDE RECEPTOR RADIONUCLIDE THERAPY AND RADIATION NEPHROPATHY

Peptide receptor radionuclide therapy (PRRT) is mainly used in the treatment of neuroendocrine tumors (NETs), which expresses somatostatin receptors. It utilizes either ^{90}Yttrium (^{90}Y) or ^{177}Lutetium (^{177}Lu) radioisotopes, which attach to a somatostatin analogue via the chelating agent, dodecane tetraacetic acid (DOTA). In contrast to external beam radiation, radiation exposure from PRRT is of low energy, lower dose and inhomogeneously distributed. These peptides are actively reabsorbed from the apical membrane of proximal tubule due to their small size and no significant protein binding. They are also internalized into the cells as opposed to rapidly washed out, hence possess delayed effects [118]. There are two phases of radiation nephropathy: An acute phase occurs at 6–18 months after radiotherapy, which manifests as new onset hypertension, proteinuria and anemia; a chronic phase occurs at least 18 months after radiation, and presents with progressive kidney impairment, hypertension, proteinuria and small atrophic kidneys on imaging [119]. Acute histopathologic changes include endothelial cell injury, TMA, mesangiolysis, whereas interstitial fibrosis, glomerular scarring, tubular atrophy and arterial sclerosis are observed in chronic phase [119,120].Severe nephrotoxicity of up to 14% have been observed in patients treated with PRRT [121]. Patients with preexisting CKD, hypertension or diabetes, concurrent use of nephrotoxic chemotherapy are at a higher risk of developing acute or delayed nephropathy.

Concurrent infusion of positive charged amino acid transporters such as L-Arginine and/or L-Lysine competitively inhibits reabsorption of the radio tracers and can lead to 9–53% reduction in radiation dose and has been the most successful technique in reducing PRRT associated nephrotoxicity [122]. Total radiation dose of less than 40 Gy is recommended for patients without risk factors, and less then 28 Gy for patients with CKD risk factors [123].

CONCLUSION

As the landscape of anticancer therapies continues to rapidly change, clinicians in both oncology and nephrology will need to recognize and manage emerging treatment-related causes of kidney injury. While novel therapies including immunotherapies and targeted treatments have improved survival outcomes, they also carry the risk of newly recognized forms of AKI (which may involve various compartments of the kidney), as well as 'pseudo-AKI'. The continual growth of drugs in the anticancer armamentarium requires that clinicians in onco-nephrology must be able to understand the various potential kidney lesions, and discern those with clinically meaningful impact on both cancer and kidney outcomes. The goal of diagnosis and management of AKI during cancer therapy should be to mitigate the sequelae of these events on optimal cancer treatment.

Table 2. Targeted therapies with known reports of pseudo acute kidney injury

Drug	Incidence of creatinine increase	Other kidney adverse events
ALK INH [124]	33%	Peripheral edema (40–50%), Hypophosphatemia (15%) [132], Formation of renal cysts (9%) [133]
Crizotinib [125,126]	26%	
	Unknown	Grade 3 Hypophosphatemia (2–4%), Grade 3 Hyponatremia [67]
Ceritinib	12%	Grade 3 Hypophosphatemia (2–4%)
Alectinib	20%	HTN (23–32%), Peripheral edema (7%), Hypokalemia (6%)
Brigatinib [127–129]		Peripheral edema (40–50%)
Lorlatinib		Edema (20%)
Ensartinib [130]		Peripheral Edema (26%), Hypophosphatemia (6%)
Entrectinib [131]		
CDK 4/6 INH [134]	12–60%	ATN, AIN [134], Hypokalemia (21%), Hyponatremia (12%)
Abemaciclib [135▪,136]	20–59%	Hypokalemia (13%), Hyponatremia (9%), Hypercalcemia (7%)
Palbociclib [137,138]	44–61%	Hypokalemia (15%), hypocalcemia (14%), Hyponatremia (15%)
Ribociclib [138,139]		
PARP INH [140]	20–30%	HTN (19%) [142]
Olaparib	20–30%	
Niraparib	11–30% [141]	
Rucaparib		
BCR-ABL INH	6–13%	
Imatinib [143–145]	1–2%	Facial and peripheral edema (24–50%)
Dasatinib [146–148]		Proteinuria (10%)
		Edema (23%)
MET INH	18%	Peripheral edema (63%)
Tepotinib [149,150]	18%	Peripheral edema (43%)
Capmatinib [151,152]		
HER2 INH	14%	N/A
Tucatinib [153]		
BRAF INH [154]	78%	AIN, ATN, hyponatremia, hypokalemia (unknown)
Vemurafenib	<1%	Hypophosphatemia (7%), Granulomatous nephritis (rare)
Dabrafenib		

AIN, acute interstitial nephritis; ALK, anaplastic lymphoma kinase; ATN, acute tubular necrosis; CDK, cyclin dependent kinase; HER, human epidermal growth factor receptor; HTN, hypertension; PARP, poly ADP ribose polymerase.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Christiansen CF, Johansen MB, Langeberg WJ, *et al.* Incidence of acute kidney injury in cancer patients: a Danish population-based cohort study. Eur J Intern Med 2011; 22:399–406.
2. Kitchlu A, McArthur E, Amir E, *et al.* Acute kidney injury in patients receiving systemic treatment for cancer: a population-based cohort study. J Natl Cancer Inst 2019; 111:727–736.
3. Manohar S, Leung N. Cisplatin nephrotoxicity: a review of the literature. J Nephrol 2018; 31:15–25.
4. Goldstein RS, Mayor GH. Minireview. The nephrotoxicity of cisplatin. Life Sci 1983; 32:685–690.
5. Bhat ZY, Cadnapaphornchai P, Ginsburg K, *et al.* Understanding the risk factors and long-term consequences of cisplatin-associated acute kidney injury: an observational cohort study. PloS One 2015; 10:e0142225.
6. van der Vorst MJDL, Neefjes ECW, Toffoli EC, *et al.* Incidence and risk factors for acute kidney injury in head and neck cancer patients treated with concurrent chemoradiation with high-dose cisplatin. BMC Cancer 2019; 19:1066.
7. Shinke H, Masuda S, Togashi Y, *et al.* Urinary kidney injury molecule-1 and monocyte chemotactic protein-1 are noninvasive biomarkers of cisplatin-induced nephrotoxicity in lung cancer patients. Cancer Chemother Pharmacol 2015; 76:989–996.
8. Latcha S, Jaimes EA, Patil S, *et al.* Long-term renal outcomes after cisplatin treatment. Clin J Am Soc Nephrol 2016; 11:1173–1179.
9. Miyoshi T, Uoi M, Omura F, *et al.* Risk factors for cisplatin-induced nephrotoxicity: a multicenter retrospective study. Oncology 2021; 99: 105–113.
10. Ben Ayed W, Ben Said A, Hamdi A, *et al.* Toxicity, risk factors and management of cisplatin-induced toxicity: a prospective study. J Oncol Pharm Pract 2020; 26:1621–1629.
11. Motwani SS, McMahon GM, Humphreys BD, *et al.* Development and validation of a risk prediction model for acute kidney injury after the first course of cisplatin. J Clin Oncol 2018; 36:682–688.
12. Tang C, Livingston MJ, Safirstein R, Dong Z. Cisplatin nephrotoxicity: new insights and therapeutic implications. Nat Rev Nephrol 2023; 19: 53–72.

13. Motwani SS, Kaur SS, Kitchlu A. Cisplatin nephrotoxicity: novel insights into mechanisms and preventive strategies. Semin Nephrol 2022; 42: 151341.
14. Selim MS, Kassem AB, El-Bassiouny NA, *et al.* Polymorphic renal transporters and cisplatin's toxicity in urinary bladder cancer patients: current perspectives and future directions. Med Oncol 2023; 40:80.
15. Dasari S, Tchounwou PB. Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol 2014; 740:364–378.
16. Kuhlmann MK, Burkhardt G, Köhler H. Insights into potential cellular mechanisms of cisplatin nephrotoxicity and their clinical application. Nephrol Dial Transplant 1997; 12:2478–2480.
17. Crona DJ, Faso A, Nishijima TF, *et al.* A systematic review of strategies to prevent cisplatin-induced nephrotoxicity. Oncologist 2017; 22:609–619.
18. Zhang J, Zhou W. Ameliorative effects of SLC22A2 gene polymorphism 808 G/T and cimetidine on cisplatin-induced nephrotoxicity in Chinese cancer patients. Food Chem Toxicol 2012; 50:2289–2293.
19. Ghonaim E, El-Haggar S, Gohar S. Possible protective effect of pantoprazole against cisplatin-induced nephrotoxicity in head and neck cancer patients: a randomized controlled trial. Med Oncol 2021; 38:108.
20. Saito Y, Okamoto K, Kobayashi M, *et al.* Magnesium attenuates cisplatin-induced nephrotoxicity by regulating the expression of renal transporters. Eur J Pharmacol 2017; 811:191–198.
21. Suppadungsuk S, Phitakwatchara W, Reungwetwattana T, *et al.* Preloading magnesium attenuates cisplatin-associated nephrotoxicity: pilot randomized controlled trial (PRAGMATIC study). ESMO Open 2022; 7:100351.
22. Guo X, Xu L, Velazquez H, *et al.* Kidney-targeted renalase agonist prevents cisplatin-induced chronic kidney disease by inhibiting regulated necrosis and inflammation. J Am Soc Nephrol 2022; 33:342–356.
23. Xu S, Jia P, Fang Y, *et al.* Nuclear farnesoid X receptor attenuates acute kidney injury through fatty acid oxidation. Kidney Int 2022; 101:987–1002.
24. Li Y, Shi L, Zhao F, *et al.* PIM1 attenuates cisplatin-induced AKI by inhibiting Drp1 activation. Cell Signal 2024; 113:110969.
25. Hu Z, Zhang H, Yi B, *et al.* VDR activation attenuate cisplatin induced AKI by inhibiting ferroptosis. Cell Death Dis 2020; 11:73.
26. ▪ Pushpan CK, Kresock DF, Ingersoll MA, *et al.* Repurposing AZD5438 and dabrafenib for cisplatin-induced AKI. J Am Soc Nephrol 2024; 35:22–40.
Novel use of repurposed therapeutics, AZD5438 and dabrafenib, for nephroprotection from cisplatin.
27. Gupta S, Portales-Castillo I, Daher A, Kitchlu A. Conventional chemotherapy nephrotoxicity. Adv Chronic Kidney Dis 2021; 28:402–414; e1.
28. Duan ZY, Liu JQ, Yin P, *et al.* Impact of aging on the risk of platinum-related renal toxicity: a systematic review and meta-analysis. Cancer Treat Rev 2018; 69:243–253.
29. Skinner R, Parry A, Price L, *et al.* Persistent nephrotoxicity during 10-year follow-up after cisplatin or carboplatin treatment in childhood: relevance of age and dose as risk factors. Eur J Cancer 19902009; 45:3213–3219.
30. Labaye J, Sarret D, Duvic C, *et al.* Renal toxicity of oxaliplatin. Nephrol Dial Transplant 2005; 20:1275–1276.
31. Guan J, Li Q, Zhang Y, *et al.* A meta-analysis comparing cisplatin-based to carboplatin-based chemotherapy in moderate to advanced squamous cell carcinoma of head and neck (SCCHN). Oncotarget 2016; 7:7110–7119.
32. Howard SC, McCormick J, Pui CH, *et al.* Preventing and managing toxicities of high-dose methotrexate. Oncologist 2016; 21:1471–1482.
33. Howell SB, Carmody J. Changes in glomerular filtration rate associated with high-dose methotrexate therapy in adults. Cancer Treat Rep 1977; 61: 1389–1391.
34. Tsurusawa M, Gosho M, Mori T, *et al.* Statistical analysis of relation between plasma methotrexate concentration and toxicity in high-dose methotrexate therapy of childhood non-Hodgkin lymphoma. Pediatr Blood Cancer 2015; 62:279–284.
35. May J, Carson KR, Butler S, *et al.* High incidence of methotrexate associated renal toxicity in patients with lymphoma: a retrospective analysis. Leuk Lymphoma 2014; 55:1345–1349.
36. Wight J, Ku M, Garwood M, *et al.* Toxicity associated with high-dose intravenous methotrexate for hematological malignancies. Leuk Lymphoma 2022; 63:2375–2382.
37. Jiang R, Mei S, Zhao Z. Leucovorin (folinic acid) rescue for high-dose methotrexate: a review. J Clin Pharm Ther 2022; 47:1452–1460.
38. Song Z, Hu Y, Liu S, *et al.* Medication therapy of high-dose methotrexate: an evidence-based practice guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. Br J Clin Pharmacol 2022; 88:2456–2472.
39. Mosleh E, Snyder S, Wu N, *et al.* Factors influencing delayed clearance of high dose methotrexate (HDMTX) in pediatric, adolescent, and young adult oncology patients. Front Oncol 2023; 13:1280587.
40. Sakran R, Milo G, Jabareen A, *et al.* Effective elimination of high-dose methotrexate by repeated hemodiafiltration and high-flux hemodialysis in patients with acute kidney injury. J Oncol Pharm Pract 2022; 28:508–515.
41. ■■ Ghannoum M, Roberts DM, Goldfarb DS, *et al.* Extracorporeal treatment for methotrexate poisoning: systematic review and recommendations from the EXTRIP Workgroup. Clin J Am Soc Nephrol 2022; 17:602–622.
Clinical recommendations for the management of nephrotoxicity from high-dose methotrexate.
42. Gros L, Roldán A, Cabero-Martínez A, *et al.* Incidence and management of patients with methotrexate delayed elimination in the clinical practice: a Delphi study. J Oncol Pharm Pract 2023; 29:794–801.
43. Ramsey LB, Balis FM, O'Brien MM, *et al.* Consensus guideline for use of glucarpidase in patients with high-dose methotrexate induced acute kidney injury and delayed methotrexate clearance. Oncologist 2018; 23:52–61.
44. Adjei AA. Pharmacology and mechanism of action of pemetrexed. Clin Lung Cancer 2004; 5(Suppl 2):S51–S55.
45. Rombolà G, Vaira F, Trezzi M, *et al.* Pemetrexed induced acute kidney injury in patients with nonsmall cell lung cancer: reversible and chronic renal damage. J Nephrol 2015; 28:187–191.
46. He Q, Bi X, Ren C, *et al.* Phase II study of the efficacy and safety of high-dose pemetrexed in combination with cisplatin versus temozolomide for the treatment of nonsmall cell lung cancer with brain metastases. Anticancer Res 2017; 37:4711–4716.
47. de Rouw N, Boosman RJ, van de Bruinhorst H, *et al.* Cumulative pemetrexed dose increases the risk of nephrotoxicity. Lung Cancer 2020; 146:30–35.
48. Sbitti Y, Chahdi H, Slimani K, *et al.* Renal damage induced by pemetrexed causing drug discontinuation: a case report and review of the literature. J Med Case Rep 2017; 11:182.
49. Glezerman IG, Pietanza MC, Miller V, Seshan SV. Kidney tubular toxicity of maintenance pemetrexed therapy. Am J Kidney Dis 2011; 58:817–820.
50. Vootukuru V, Liew YP, Nally JV. Pemetrexed-induced acute renal failure, nephrogenic diabetes insipidus, and renal tubular acidosis in a patient with nonsmall cell lung cancer. Med Oncol 2006; 23:419–422.
51. Chauvet S, Courbebaisse M, Ronco P, Plaisier E. Pemetrexed-induced acute kidney injury leading to chronic kidney disease. Clin Nephrol 2014; 82:402–406.
52. Kawazoe H, Yano A, Ishida Y, *et al.* Nonsteroidal anti-inflammatory drugs induce severe hematologic toxicities in lung cancer patients receiving pemetrexed plus carboplatin: a retrospective cohort study. PLoS One 2017; 12:e0171066.
53. Ando Y, Hayashi T, Ujita M, *et al.* Effect of renal function on pemetrexed-induced haematotoxicity. Cancer Chemother Pharmacol 2016; 78:183–189.
54. Dumoulin DW, Visser S, Cornelissen R, *et al.* Renal toxicity from pemetrexed and pembrolizumab in the era of combination therapy in patients with metastatic nonsquamous cell NSCLC. J Thorac Oncol 2020; 15:1472–1483.
55. Casper ES, Green MR, Kelsen DP, *et al.* Phase II trial of gemcitabine (2,2′-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. Invest New Drugs 1994; 12:29–34.
56. Walter RB, Joerger M, Pestalozzi BC. Gemcitabine-associated hemolytic-uremic syndrome. Am J Kidney Dis 2002; 40:E16.
57. Glezerman I, Kris MG, Miller V, *et al.* Gemcitabine nephrotoxicity and hemolytic uremic syndrome: report of 29 cases from a single institution. Clin Nephrol 2009; 71:130–139.
58. Daviet F, Rouby F, Poullin P, *et al.* Thrombotic microangiopathy associated with gemcitabine use: presentation and outcome in a national French retrospective cohort. Br J Clin Pharmacol 2019; 85:403–412.
59. Nishikubo M, Shimomura Y, Hiramoto N, *et al.* Reversible renal-limited thrombotic microangiopathy due to gemcitabine-dexamethasone-cisplatin therapy: a case report. BMC Nephrol 2021; 22:175.
60. Krishnappa V, Gupta M, Shah H, *et al.* The use of eculizumab in gemcitabine induced thrombotic microangiopathy. BMC Nephrol 2018; 19:9.
61. Grall M, Daviet F, Chiche NJ, *et al.* Eculizumab in gemcitabine-induced thrombotic microangiopathy: experience of the French thrombotic microangiopathies reference centre. BMC Nephrol 2021; 22:267.
62. Ensergueix G, Pallet N, Joly D, *et al.* Ifosfamide nephrotoxicity in adult patients. Clin Kidney J 2020; 13:660–665.
63. Skinner R, Sharkey IM, Pearson AD, Craft AW. Ifosfamide, mesna, and nephrotoxicity in children. J Clin Oncol 1993; 11:173–190.
64. Gupta S, Cortazar FB, Riella LV, Leaf DE. Immune checkpoint inhibitor nephrotoxicity: update. Kidney360 2020; 1:130–140.
65. Seethapathy H, Herrmann SM, Sise ME. Immune Checkpoint Inhibitors and Kidney Toxicity: Advances in Diagnosis and Management. Kidney Med 2021; 3:1074–1081.
66. Seethapathy H, Zhao S, Chute DF, *et al.* The incidence, causes, and risk factors of acute kidney injury in patients receiving immune checkpoint inhibitors. Clin J Am Soc Nephrol 2019; 14:1692–1700.
67. Cortazar FB, Kibbelaar ZA, Glezerman IG, *et al.* Clinical features and outcomes of immune checkpoint inhibitor–associated AKI: a multicenter study. J Am Soc Nephrol 2020; 31:435–446.
68. Gupta S, Short SAP, Sise ME, *et al.* Acute kidney injury in patients treated with immune checkpoint inhibitors. J Immunother Cancer 2021; 9:e003467.
69. Munch PV, Nørgaard M, Heide-Jørgensen U, *et al.* Proton pump inhibitors and the risk of acute kidney injury in cancer patients receiving immune checkpoint inhibitors: A Danish population-based cohort study. Int J Cancer 2024; 154:1164–1173.
70. ▪ Che JJ, Lee TH, Kuo G, *et al.* All-cause and immune checkpoint inhibitor–associated acute kidney injury in immune checkpoint inhibitor users: a meta-analysis of occurrence rate, risk factors and mortality. Clinical Kidney J 2024; 17: sfad292.
Large meta-analysis of ICI-associated AKI incidence, risk factors and outcomes (including mortality).

71. Kitchlu A, Jhaveri KD, Wadhwani S, *et al.* A systematic review of immune checkpoint inhibitor–associated glomerular disease. Kidney Int Rep 2021; 6:66–77.
72. Qualls D, Seethapathy H, Bates H, *et al.* Positron emission tomography as an adjuvant diagnostic test in the evaluation of checkpoint inhibitor-associated acute interstitial nephritis. J Immunother Cancer 2019; 7:356.
73. Isik B, Alexander MP, Manohar S, *et al.* Biomarkers, clinical features, and rechallenge for immune checkpoint inhibitor renal immune-related adverse events. Kidney Int Rep 2021; 6:1022–1031.
74. ■ Sise ME, Wang Q, Seethapathy H, *et al.* Soluble and cell-based markers of immune checkpoint inhibitor-associated nephritis. J Immunother Cancer 2023; 11:e006222.

Retrospective cohort showing potential of soluble interleukin-2 receptor alpha and flow cytometry markers of B-cell and T-cell dysregulation may assist in diagnosis of ICI nephritis.

75. ■■ Moledina DG, Obeid W, Smith RN, *et al.* Identification and validation of urinary CXCL9 as a biomarker for diagnosis of acute interstitial nephritis. J Clin Invest 2023; 133:e168950.

Important prospective cohort study of biopsy-proven acute interstitial nephritis first identifying urinary CXCL9 as a potential biomarker.

76. Lee MD, Seethapathy H, Strohbehn IA, *et al.* Rapid corticosteroid taper versus standard of care for immune checkpoint inhibitor induced nephritis: a single-center retrospective cohort study. J Immunother Cancer 2021; 9: e002292.
77. Gupta S, Garcia-Carro C, Prosek JM, *et al.* Shorter versus longer corticosteroid duration and recurrent immune checkpoint inhibitor-associated AKI. J Immunother Cancer 2022; 10:e005646.
78. Miao J, Sise ME, Herrmann SM. Immune checkpoint inhibitor related nephrotoxicity: advances in clinicopathologic features, noninvasive approaches, and therapeutic strategy and rechallenge. Front Nephrol 2022; 2:1017921.
79. Lin JS, Mamlouk O, Selamet U, *et al.* Infliximab for the treatment of patients with checkpoint inhibitor associated acute tubular interstitial nephritis. Oncolmmunology 2021; 10:1877415.
80. Jessel S, Austin M, Kluger HM. Mycophenolate as primary treatment for immune checkpoint inhibitor induced acute kidney injury in a patient with concurrent immunotherapy-associated diabetes: A case report. Clin Oncol Case Rep 2021; 4:156.
81. Kanbay M, Copur S, Siriopol D, *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.
82. Gupta S, Seethapathy H, Strohbehn IA, *et al.* Acute kidney injury and electrolyte abnormalities after chimeric antigen receptor T-cell (CAR-T) therapy for diffuse large B-cell lymphoma. Am J Kidney Dis 2020; 76:63–71.
83. Gutgarts V, Jain T, Zheng J, *et al.* Acute kidney injury after CAR-T cell therapy: low incidence and rapid recovery. Biol Blood Marrow Transplant 2020; 26:1071–1076.
84. Khan I, Khan N, Wolfson N, *et al.* Safety of CAR-T cell therapy in patients with renal failure/acute kidney injury: focused review. Clin Hematol Int 2023; 5(2–3):122–129.
85. Hunter BD, Hoda D, Nguyen A, *et al.* Successful administration of chimeric antigen receptor (CAR) T-cell therapy in patients requiring hemodialysis. Exp Hematol Oncol 2022; 11:10.
86. Ahmed G, Bhasin-Chhabra B, Szabo A, *et al.* Impact of chronic kidney disease and acute kidney injury on safety and outcomes of CAR T-cell therapy in lymphoma patients. Clin Lymphoma Myeloma Leuk 2022; 22:863–868.
87. Wood AC, Perez AP, Arciola B, *et al.* Outcomes of CD19-targeted chimeric antigen receptor T cell therapy for patients with reduced renal function including dialysis. Transplant Cell Ther 2022; 28:829; e1-829.e8.
88. Izzedine H, Rixe O, Billemont B, *et al.* Angiogenesis inhibitor therapies: focus on kidney toxicity and hypertension. Am J Kidney Dis 2007; 50:203–218.
89. An MM, Zou Z, Shen H, *et al.* Incidence and risk of significantly raised blood pressure in cancer patients treated with bevacizumab: an updated meta-analysis. Eur J Clin Pharmacol 2010; 66:813–821.
90. Jin K, Shen Y, He K, *et al.* Aflibercept (VEGF Trap): one more double-edged sword of anti-VEGF therapy for cancer? Clin Transl Oncol 2010; 12:526–532.
91. Zhang W, Feng LJ, Teng F, *et al.* Incidence and risk of proteinuria associated with newly approved vascular endothelial growth factor receptor tyrosine kinase inhibitors in cancer patients: an up-to-date meta-analysis of randomized controlled trials. Expert Rev Clin Pharmacol 2020; 13:311–320.
92. Zhang ZF, Wang T, Liu LH, Guo HQ. Risks of proteinuria associated with vascular endothelial growth factor receptor tyrosine kinase inhibitors in cancer patients: a systematic review and meta-analysis. PLoS One 2014; 9:E90135.
93. Kala J, Salman LA, Geara AS, Izzedine H. Nephrotoxicity from molecularly targeted chemotherapeutic agents. Adv Chronic Kidney Dis 2021; 28: 415–428.
94. Kumasaka R, Nakamura N, Shirato K, *et al.* Side effects of therapy: case 1. Nephrotic syndrome associated with gefitinib therapy. J Clin Oncol 2004; 22:2504–2505.
95. Maruyama K, Chinda J, Kuroshima T, *et al.* Minimal change nephrotic syndrome associated with gefitinib and a successful switch to erlotinib. Intern Med 2015; 54:823–826.
96. Masutani K, Fujisaki K, Maeda H, *et al.* Tubulointerstitial nephritis and IgA nephropathy in a patient with advanced lung cancer treated with long-term gefitinib. Clin Exp Nephrol 2008; 12:398–402.
97. Kurita N, Mise N, Fujii A, *et al.* Crescentic glomerulonephritis in a patient with advanced lung cancer during erlotinib therapy. NDT Plus 2009; 2:512–513.
98. Izzedine H, Boostandoost H, Mathian A. Panitumumab-induced immune complex glomerulonephritis. Am J Kidney 2017; 69:320–321.
99. Niitsu T, Hayashi T, Uchida J, *et al.* Drug-Induced Kidney Injury Caused by Osimertinib: Report of a Rare Case. Nephron 2022; 146:58–63.
100. Wanchoo R, Jhaveri KD, Deray G, Launay-Vacher V. Renal effects of BRAF inhibitors: a systematic review by the cancer and the kidney international network. Clin Kidney J 2016; 9:245–251.
101. Teuma C, Pelletier S, Amini-Adl M, *et al.* Adjunction of a MEK inhibitor to Vemurafenib in the treatment of metastatic melanoma results in a 60% reduction of acute kidney injury. Cancer Chemother Pharmacol 2017; 79:1043–1049.
102. Seethapathy H, Bates H, Chute DF, *et al.* Acute kidney injury following Encorafenib and binimetinib for metastatic melanoma. Kidney Med 2020; 2:373–375.
103. Martino S, Daguindau E, Ferrand C, *et al.* A successful renal transplantation for renal failure after dasatinib-induced thrombotic thrombocytopenic purpura in a patient with imatinib-resistant chronic myelogenous leukaemia on nilotinib. Leuk Res Rep 2013; 2:29–31.
104. Hirano T, Hashimoto M, Korogi Y - b, *et al.,* Department of Nephrology. Kumamoto City Hospital. Dasatinib-induced nephrotic syndrome. Leuk Lymphoma 2016; 57:726–727.
105. Wallace E, Lyndon W, Chumley P, *et al.* Dasatinib-induced nephrotic-range proteinuria. Am J Kidney 2013; 61:1026–1031.
106. Jhaveri KD, Chidella S, Varghese J, *et al.* Carfilzomib-related acute kidney injury. Clin Adv Hematol Oncol 2013; 11:604–605.
107. Wanchoo R, Khan S, Kolitz JE, Jhaveri KD. Carfilzomib-related acute kidney injury may be prevented by N-acetyl-L-cysteine. J Oncol Pharm Pr 2015; 21:313–316.
108. Shely RN, Ratliff PD. Carfilzomib-associated tumor lysis syndrome. Pharmacotherapy 2014; 34:e34–e37.
109. Yui JC, Van Keer J, Weiss BM, *et al.* Proteasome inhibitor associated thrombotic microangiopathy. Am J Hematol 2016; 91:E348.
110. Glezerman IG, Kewalramani T, Jhaveri K. Reversible Fanconi syndrome due to lenalidomide. NDT Plus 2008; 1:215–217.
111. Shaaban H, Layne T, Guron G. A case of DRESS (drug reaction with eosinophilia and systemic symptoms) with acute interstitial nephritis secondary to lenalidomide. J Oncol Pharm Pr 2014; 20:302–304.
112. Jamme M, Galichon P, Hertig A. Minimal change disease and lenalidomide. Am J Kidney Dis 2013; 62:844.
113. Lipson EJ, Huff CA, Holanda DG, *et al.* Lenalidomide-induced acute interstitial nephritis. Oncologist 2010; 15:961.
114. Vanhoutte T, Sprangers B. Pseudo-AKI associated with targeted anticancer agents-the truth is in the eye of the filtration marker. Clin Kidney J 2023; 16:603–610.
115. ■ Chen MF, Harada G, Liu D, *et al.* Brief report: tyrosine kinase inhibitors for lung cancers that inhibit MATE-1 can lead to "False" decreases in renal function. J Thorac Oncol 2024; 19:153–159.

Large retrospective cohort of patients receiving various tyrosine kinase inhibitors associated with pseudo-AKI.

116. Ciarimboli G, Lancaster CS, Schlatter E, *et al.* Proximal tubular secretion of creatinine by organic cation transporter OCT2 in cancer patients. Clin Cancer Res 2012; 18:1101–1108.
117. Malyszko J, Lee MW, Capasso G, *et al.* How to assess kidney function in oncology patients. Kidney Int 2020; 97:894–903.
118. Parihar AS, Chopra S, Prasad V. Nephrotoxicity after radionuclide therapies. Transl Oncol 2022; 15:101295.
119. Klaus R, Niyazi M, Lange-Sperandio B. Radiation-induced kidney toxicity: molecular and cellular pathogenesis. Radiat Oncol 2021; 16:; https://doi.org/10.1186/s13014-021-01764-y.
120. Cohen EP. Radiation nephropathy after bone marrow transplantation. Kidney Int 2000; 58:903–918.
121. Moulder JE, Cohen EP. Radiation-induced multi-organ involvement and failure: the contribution of radiation effects on the renal system. British J Radiology 2005; 78(Suppl_27):82–88.
122. Bernard BF, Krenning EP, Breeman WA, *et al.* D-lysine reduction of indium-111 octreotide and yttrium-90 octreotide renal uptake. J Nucl Med 1997; 38:1929–1933.
123. Bodei L, Cremonesi M, Ferrari M, *et al.* Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with 90Y-DOTATOC and 177Lu-DOTATATE: the role of associated risk factors. Eur J Nucl Med Mol Imaging 2008; 35:1847–1856.
124. Bonilla M, Jhaveri KD, Izzedine H. Anaplastic lymphoma kinase inhibitors and their effect on the kidney. Clin Kidney J 2022; 15:1475–1482.
125. Brosnan EM, Weickhardt AJ, Lu X, *et al.* Drug-induced reduction in estimated glomerular filtration rate in patients with ALK-positive nonsmall cell lung cancer treated with the ALK inhibitor crizotinib. Cancer 2014; 120:664–674.

126. Shaw AT, Ou SHI, Bang YJ, *et al.* Crizotinib in ROS1-rearranged nonsmall-cell lung cancer. N Engl J Med 2014; 371:1963–1971.
127. Camidge DR, Kim HR, Ahn MJ, *et al.* Brigatinib versus crizotinib in ALK inhibitor-naive advanced ALK-positive NSCLC: final results of Phase 3 ALTA-1L trial. J Thorac Oncol 2021; 16:2091–2108.
128. Camidge DR, Kim HR, Ahn MJ, *et al.* Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. N Engl J Med 2018; 379:2027–2039.
129. Camidge DR, Kim HR, Ahn MJ, *et al.* Brigatinib versus crizotinib in advanced ALK inhibitor-naive ALK-positive Non-small cell lung cancer: second interim analysis of the Phase III ALTA-1L trial. J Clin Oncol 2020; 38:3592–3603.
130. Horn L, Wang Z, Wu G, *et al.* Ensartinib vs crizotinib for patients with anaplastic lymphoma kinase-positive non-Small cell lung cancer: a randomized clinical trial. JAMA Oncol 2021; 7:1617–1625.
131. Doebele RC, Drilon A, Paz-Ares L, *et al.* Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020; 21:271–282.
132. Crinò L, Ahn MJ, De Marinis F, *et al.* Multicenter Phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non-small-cell lung cancer previously treated with chemotherapy and crizotinib: results from ASCEND-2. J Clin Oncol 2016; 34:2866–2873.
133. Schnell P, Bartlett CH, Solomon BJ, *et al.* Complex renal cysts associated with crizotinib treatment. Cancer Med 2015; 4:887–896.
134. Gupta S, Caza T, Herrmann SM, *et al.* Clinicopathologic features of acute kidney injury associated with CDK4/6 inhibitors. Kidney Int Rep 2022; 7:618–623.
135. Hanna PE, Strohbehn IA, Moreno D, *et al.* Adverse kidney outcomes of CDK ■ 4/6 inhibitors for metastatic breast cancer. NPJ Breast Cancer 2023; 9:70.
Large retrospective cohort of kidney function changes (i.e., pseudo-AKI) after initiation of cyclin-dependent kinase (CDK) 4/6 inhibitors for breast cancer.
136. Chappell JC, Turner PK, Pak YA, *et al.* Abemaciclib inhibits renal tubular secretion without changing glomerular filtration rate. Clin Pharmacol Ther 2019; 105:1187–1195.
137. Mach T, Qi A, Bouganim N, Trinh E. Targeted cancer therapies causing elevations in serum creatinine through tubular secretion inhibition: a case report and review of the literature. Can J Kidney Health Dis 2022; 9:20543581221106246.
138. Keskinkılıç M, Semiz HS, Yavuzsen T, Karaoglu A. 194P Increased blood creatinine level due to CDK 4/6 inhibitor treatments: single center experience. Ann Oncol 2022; 33:S216.
139. Wilson BE, Mok K, Kiely BE, *et al.* Association between ribociclib and changes in creatinine in patients with hormone receptor positive metastatic breast cancer. Intern Med J 2019; 49:1438–1442.
140. Zibetti Dal Molin G, Westin SN, Msaouel P, *et al.* Discrepancy in calculated and measured glomerular filtration rates in patients treated with PARP inhibitors. Int J Gynecol Cancer 2020; 30:89–93.
141. Monk BJ, Parkinson C, Lim MC, *et al.* A randomized, phase III trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). J Clin Oncol 2022; 40:3952–3964.
142. Mirza MR, Monk BJ, Herrstedt J, *et al.* Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 2016; 375:2154–2164.
143. Vidal-Petiot E, Rea D, Serrano F, *et al.* Imatinib increases serum creatinine by inhibiting its tubular secretion in a reversible fashion in chronic myeloid leukemia. Clin Lymphoma Myeloma Leuk 2016; 16:169–174.
144. Singh AK, Hussain S, Ahmed R, *et al.* Impact of imatinib treatment on renal function in chronic myeloid leukaemia patients. Nephrol Carlton Vic 2022; 27:318–326.
145. Schlemmer M, Bauer S, Schütte R, *et al.* Activity and side effects of imatinib in patients with gastrointestinal stromal tumors: data from a German multicenter trial. Eur J Med Res 2011; 16:206–212.
146. Adegbite BO, Abramson MH, Gutgarts V, *et al.* Patient-specific pharmacokinetics and dasatinib nephrotoxicity. Clin J Am Soc Nephrol 2023; 18:1175–1185.
147. Radich JP, Kopecky KJ, Appelbaum FR, *et al.* A randomized trial of dasatinib 100 mg versus imatinib 400 mg in newly diagnosed chronic-phase chronic myeloid leukemia. Blood 2012; 120:3898–3905.
148. Yilmaz M, Lahoti A, O'Brien S, *et al.* Estimated glomerular filtration rate changes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. Cancer 2015; 121:3894–3904.
149. Wijtvliet V, Roosens L, De Bondt C, *et al.* Pseudo-acute kidney injury secondary to tepotinib. Clin Kidney J 2023; 16:760–761.
150. Paik PK, Felip E, Veillon R, *et al.* Tepotinib in non-small-cell lung cancer with MET Exon 14 skipping mutations. N Engl J Med 2020; 383:931–943.
151. Mohan A, Herrmann SM. Capmatinib-induced pseudo-acute kidney injury: a case report. Am J Kidney Dis 2022; 79:120–124.
152. Wolf J, Seto T, Han JY, *et al.* Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. N Engl J Med 2020; 383:944–957.
153. Topletz-Erickson AR, Lee AJ, Mayor JG, *et al.* Tucatinib inhibits renal transporters OCT2 and MATE without impacting renal function in healthy subjects. J Clin Pharmacol 2021; 61:461–471.
154. Wanchoo R, Jhaveri KD, Deray G, Launay-Vacher V. Renal effects of BRAF inhibitors: a systematic review by the Cancer and the Kidney International Network. Clin Kidney J 2016; 9:245–251.