Anti cancer treatment nephrotoxicity

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Chemotherapy nephrotoxicity

One study estimated that potentially nephrotoxic drugs were used in 80 percent of chemotherapy sessions.

The relation that connects cancer and renal damage is bidirectional and this renal damage worsens quality of life and increases morbidity in patients with cancer and kidney injury.

Etiologies of acute kidney injury in the cancer patient

Prerenal causes	Intrinsic renal causes	Postrenal causes
■ Volume depletion • Decreased oral intake • Gastrointestinal losses ■ Sepsis ■ Hypercalcemia ■ Medications • ACE inhibitors or angiotensin receptor blockers • Diuretics • Iodinated contrast • NSAIDs ■ Sinusoidal obstruction syndrome (venoocclusive disease)	■ Glomerular • Monoclonal gammopathy-associated proliferative glomerulonephritis • Rapidly progressive glomerulonephritis ■ Tubulointerstitial • Acute interstitial nephritis • Acute tubular necrosis • Light chain cast nephropathy • Lysozymuria • Nephrotoxic anticancer agents • Tumor infiltration of the kidney • Tumor lysis syndrome ■ Vascular • Thrombotic microangiopathy	■ Obstructive uropathy ■ Retroperitoneal fibrosis

ACE: angiotensin-converting enzyme; NSAIDs: nonsteroidal anti-inflammatory drugs.

Renal effects of anticancer drugs

AKI;
CKD;
Electrolyte disturbance;
Fanconi's syndrome;
Hypertension;
Interstitial nephritis;
Nephrolithiasis;
Nephrotic syndrome;
Renal cysts;
SIADH;
TMA.

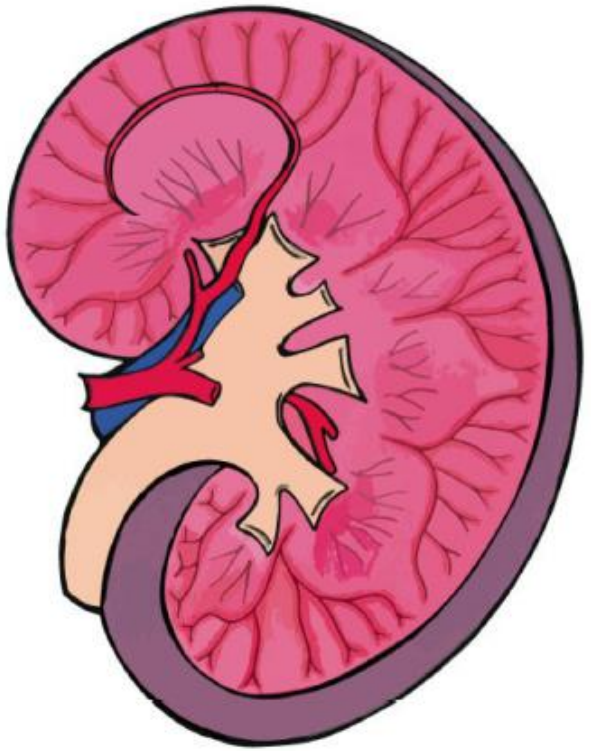


Figure 1 Renal effects of anticancer drugs. AKI: Acute kidney injury; CKD: Chronic kidney disease; SIADH: Syndrome of inappropriate antidiuretic hormone secretion; TMA: Thrombotic microangiopathy.

RISK FACTORS FOR NEPHROTOXICITY

Intravascular volume depletion, either due to external losses or fluid sequestration (as in ascites or edema).

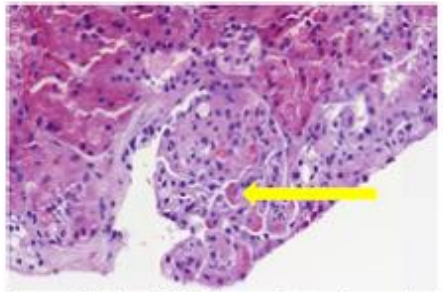
The concomitant use of nonchemotherapeutic nephrotoxic drugs (aminoglycoside antibiotics, NSAIDs, PPI, Radio contrast)

Urinary tract obstruction secondary to the underlying tumor.

Intrinsic kidney disease that is idiopathic, related to other comorbidities, age related, or related to the cancer itself.

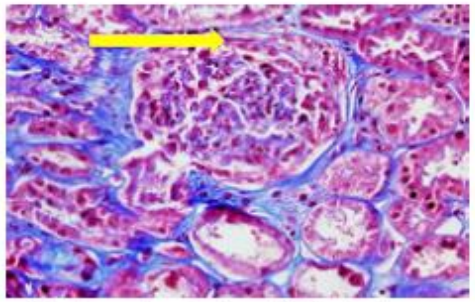
Glomerular patterns

- **Thrombotic microangiopathy**: platinum compounds, gemcitabine, mitomycin C, anti VEGF, tyrosine kinase inhibitors, interferon, check-point inhibitors

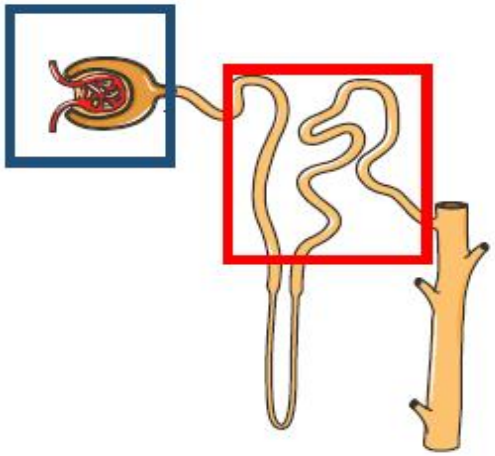


Bevacizumab-induced TMA (arrow: intraglomerular thrombi)

- **Focal segmental glomerulosclerosis**: tyrosine kinase inhibitors, interferon
- **Minimal change disease**: check-point inhibitors
- **Lupus-like nephritis**: check-point inhibitors
- **Necrotizing glomerulonephritis/vasculitis**: check-point inhibitors

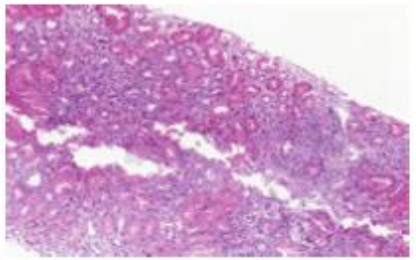


Pauciimmune extracapillar glomerulonephritis related to check-point inhibitrs (arrow: epothelial crescent)



Tubulointerstitial patterns

- **Acute/chronic interstitial nephritis**: tyrosine kinase inhibitors, BRAF inhibitors, check-point inhibitors



Dabrafenib – related acute tubulointerstitial nephritis

- **Acute tubular injury**: platinum compounds, methotrexate, pemetrexed, tyrosine kinase inhibitors, BRAF inhibitors, BRC-Abl tyrosine kinase inhibitors, CAR-T cells
- **Interstitial fibrosis and tubular atrophy**: pemetrexed
- **Uric acid nephropathy**: rituximab, CAR-T cells
- **Cristally nephropathy**: methotrexate

Fig. 1. Glomerular and tubular patterns of anticancer drug-related kidney injury.

ALKYLATING AGENTS

The main urologic toxicity of cyclophosphamide is hemorrhagic cystitis.

Similar to cyclophosphamide, the predominant toxicity of ifosfamide on the urinary tract is hemorrhagic cystitis. However, nephrotoxicity is more likely with ifosfamide than with cyclophosphamide. Ifosfamide nephrotoxicity affects the proximal tubule.(fanconi sx.) especially when combined with platinum drugs, and can progress to CKD.

When ATN occurs in the context of ifosfamide treatment, a special histological feature might be found by optical microscope the presence of karyomegalic cells. Karyomegalic changes in tubular epithelial cells result from aberrant cell division related to exposure to the toxic ifosfamide, secondarily inducing interstitial inflammation.

Conventional Chemotherapy: Platinum Compounds

Cisplatin is a widely used and highly effective cancer chemotherapeutic agent. It has been mainly related to reversible AKI approximately 3–5 days after drug exposure, although repeated doses (>100 mg/m2) may cause a permanent kidney injury.

Besides AKI, cisplatin has been also associated with proximal tubulopathy, and less frequently with thrombotic microangiopathy.

Platinum Compounds

Accurate hydration remains the main fundamental strategy for reducing the risk of cisplatin-induced nephrotoxicity. Interestingly, magnesium supplementation may have a role as a nephroprotective agent, and forced diuresis with mannitol may be appropriate in some patients receiving cisplatin.

Carboplatin and oxaliplatin, are the second and third generation of platinum agents, respectively. They are less nephrotoxic than cisplatin but can still cause AKI in patients with lower albumin (higher unbound fraction of platinum resulting in greater peak plasma concentrations), preexisting kidney damage, and concurrent use of nephrotoxic medications.

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Gemcitabine, mitomycin C, and platinum compounds were categorized by Izzedine and Perazella as "Type I" cancer drug TMA and anti-vascular endothelial growth factor (VEGF) agents (discussed below) as "Type II" cancer drug TMA, on the basis of their different mechanisms of kidney injury and outcomes.

In type I, endothelial injury and/or microvascular thrombosis are involved in the pathogenesis; it has been related to cumulative drug dose, may present many months after beginning or ending treatment, and is refractory to therapy. In relation to renal histology, fibrin thrombi are often found in glomerular and arteriolar compartments, whereas in "Type II" only glomerular thrombi are seen.

ALKYLATING AGENTS

Trabectedin is an alkylating agent that is approved for treatment of advanced soft tissue sarcoma. Cases of kidney failure (occasionally fatal) have been reported, some of which are attributable to rhabdomyolysis.

A slowly progressive, chronic interstitial nephritis that is generally irreversible can be induced by prolonged therapy with the nitrosoureas carmustine (BiCNU), lomustine (CCNU), and streptozocin. these agents may produce nephrotoxicity through alkylation of tubular cell proteins.

ANTIMETABOLITES

Clofarabine is a purine nucleoside analog that exerts its antineoplastic effect by inhibiting DNA synthesis and the enzyme ribonucleotide reductase….

Two case reports describe severe kidney injury shortly after drug administration; one patient was found to have 4 g of proteinuria, and the other developed anuria and required dialysis. No biopsy data exist to help propose a mechanism of injury in these patients, but ribonucleoside reductase may be contributing to podocyte injury and the development of proteinuria.

The magnitude of nephrotoxicity risk is unclear. In one study, the risk of acute kidney injury (AKI) was as high as 55 percent following use of clofarabine in patients undergoing hematopoietic cell transplantation. Age was the strongest predictor of AKI.

ANTIMETABOLITES

Gemcitabine is a cell cycle-specific pyrimidine antagonist; the most common form of kidney toxicity is AKI with microangiopathic hemolytic anemia (thrombotic microangiopathy [TMA], (high mortality Rate).(0.015 to 1.4 percent) In the largest case series of TMA related to gemcitabine, authors describe new-onset or exacerbated HTN and edema as early signs of TMA. Some case reports suggest that complement inhibition with eculizumab could be a reasonable therapy when plasmapheresis failed in patients with gemcitabine associated TMA.

For patients receiving hydroxyurea, serum creatinine should be periodically reassessed during treatment. A point-of care device for measuring serum creatinine (the i-STAT system) that is used for routine testing in some clinical laboratories can give a falsely elevated creatinine measurement.

ANTIMETABOLITES

Methotrexate at doses less than 0.5 to 1 g/m2 is usually not associated with kidney toxicity unless underlying kidney dysfunction is present. By contrast, high-dose intravenous methotrexate (1 to 15 g/m2) can precipitate in the tubules and induce tubular injury; at particular risk are patients who are volume depleted and those who excrete acidic urine. Maintenance of adequate urinary output and alkalinization will lessen the probability of methotrexate precipitation.(crystalline nephropathy)

Methotrexate can also produce a transient decrease in GFR, with complete recovery within six to eight hours of discontinuing the drug. The mechanism responsible for this functional kidney impairment involves afferent arteriolar constriction or mesangial cell constriction.

After AKI occurs, the excretion of the drug is reduced and the patient can develop systemic toxicity. Several strategies as highdose of leucovorin therapy (a folate compound), prolonged hemodialysis (daily for several days, to avoid rebound), or glucarpidase (an enzyme that inactivates the drug) can be used when AKI and severe systemic toxicities developed.

ANTITUMOR ANTIBIOTICS

Anthracyclines such as daunorubicin and doxorubicin have been known to cause nephrotic syndrome with kidney lesions consistent with minimal change disease, focal segmental glomerular sclerosis not otherwise specified (NOS), or collapsing glomerulopathy.

pegylated liposomal doxorubicin has been associated with renal thrombotic microangiopathy, nephrotic syndrome, and acute kidney injury.

There is a possible association of mitomycin with drug-induced thrombotic microangiopathy that has not been definitively established. Drug discontinuation and supportive care are indicated in that case, as plasmapheresis is ineffective.

Table 1. Conventional chemotherapy and nephrotoxicity

Medication	Nephrotoxicity	Mechanism of nephrotoxicity	Prevention and management recommendations
Platinum compounds (cisplatin, carboplatin, oxaliplatin)	ATI Hypomagnesemia Nephrogenic diabetes insipidus Proximal tubulopathy TMA	Direct tubular toxicity	Hydration Magnesium supplementation Forced diuresis with mannitol
Ifosfamide	ATI Proximal tubulopathy CKD	Mitochondrial tubular toxicity	No current strategy for preventing ifosfamide nephrotoxicity NAC: some beneficial effects
Pemetrexed	ATI Proximal tubulopathy Nephrogenic diabetes insipidus	Antifolate effect that impairs DNA and RNA	Leucovorin therapy
Methotrexate	ATI Crystalline nephropathy	Direct tubular toxicity Induction of oxygen free radical formation	Volume filling/urine alkalization (pH >7.5) Leucovorin therapy Prolonged hemodialysis Glucarpidase
Gemcitabine	TMA	Endothelial injury Microvascular thrombosis	Eculizumab
Mitomycin C	TMA	Endothelial injury Microvascular thrombosis	Drug discontinuation Supportive care

ATI, acute tubular Injury; CKD, chronic kidney injury; TMA, thrombotic microangiopathy; NAC, *N*-acetylcysteine.

Chemotherapy nephrotoxicity of Molecularly targeted agents and immunotherapies

ALK INHIBITORS

Crizotinib is a kinase inhibitor that is approved for treatment of advanced anaplastic lymphoma kinase (ALK) fusion gene-positive non-small cell lung cancer. Drug-induced reductions in glomerular filtration rate (GFR) are reported in patients treated with crizotinib, mostly during the first two weeks of therapy. Some have suggested that the acute effects on creatinine clearance (CrCl) reflect an effect of the drug on creatinine excretion rather than a true reduction in GFR.

In addition, the development of complex renal cysts (3 percent) has been described in patients treated with crizotinib. Both the formation of new cysts and progression of preexisting renal cysts can occur. Cyst development appears to be reversible upon discontinuation of the drug, and spontaneous cyst regression with continuous crizotinib treatment has also been reported.

BCR-ABL AND KIT INHIBITORS

Bosutinib is a dual tyrosine kinase inhibitor (TKI) that targets both the ABL and SRC pathways. It is approved for treatment of refractory CML. Although there are no published cases of acute kidney injury (AKI), hypophosphatemia and an apparently reversible decline in glomerular filtration rate (GFR) have been reported during long-term therapy with bosutinib.

Dasatinib is a second-generation TKI used mainly in patients with imatinib-resistant CML. Rare cases of AKI have been reported with the use of this agent, including one patient who developed rhabdomyolysis and others with thrombotic microangiopathy. In addition, there have been reports of proteinuria and nephrotic syndrome occurring in patients treated with dasatinib; in all cases, proteinuria resolved upon discontinuation of the drug or switching to imatinib.(podocyte injury).

BCR-ABL AND KIT INHIBITORS

Imatinib is a small molecule first-generation TKI that targets BCR-ABL and KIT; the drug is commonly used for treatment of both CML and GIST….

Acute and chronic kidney injury have been described in patients treated with extended-duration imatinib for CML.

Leukemic infiltration into the kidney should always be considered in the differential diagnosis when a patient with CML presents with kidney impairment, regardless of the clinical stage, as the kidney failure may respond to chemotherapy.

Potential mechanisms of injury include tumor lysis syndrome, acute tubular injury, and rhabdomyolysis; inhibition of tubular secretion of creatinine may also be a contributing factor to an observed rise in serum creatinine.

BTK INHIBITORS

Ibrutinib is an orally active, covalent (irreversible) inhibitor of Bruton tyrosine kinase, a mediator of the B cell receptor signaling pathway that inhibits malignant B cell survival.(CLL)

Serious and potentially fatal cases of acute kidney injury (AKI) have occurred with ibrutinib therapy.

CHECKPOINT INHIBITOR IMMUNOTHERAPY

Checkpoint inhibitors, immunomodulatory antibodies that are used to enhance the immune system, have substantially improved the prognosis for patients with advanced melanoma and are likely to significantly improve the treatment of advanced disease in a number of other malignancies.

Acute kidney injury is a rare complication of checkpoint inhibitor immunotherapy. The most common reported underlying pathology is acute tubulointerstitial nephritis, but immune complex glomerulonephritis and thrombotic microangiopathy have also been observed.

EGFR PATHWAY INHIBITORS

Monoclonal antibodies targeting the epidermal growth factor receptor (EGFR; cetuximab and panitumumab), which are typically used for treatment of advanced colorectal cancer.

renal toxicities have been reported with cetuximab, including acute kidney injury (AKI), one case report of diffuse proliferative glomerulonephritis, and another case report of nephrotic syndrome.

EGFR, which is mainly expressed in the distal and collecting tubules, is involved in maintaining tubular integrity, and activation of EGFR leads to growth and generation of tubular epithelial cells after Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) acute tubular injury. In patients prone to experiencing kidney injury, treatment with anti-EGFR agents might be a "second hit" for the development of AKI.

EGFR PATHWAY INHIBITORS

Afatinib, erlotinib, gefitinib, dacomitinib, osimertinib, and mobocertinib are all used in the treatment of non-small cell lung cancer.

there are case reports of nephrotic syndrome with kidney biopsy findings consistent with minimal-change disease and membranous nephropathy occurring in patients treated with gefitinib.

VEGF PATHWAY INHIBITORS

Two different approaches have been used to block the vascular endothelial growth factor (VEGF) pathway: VEGF ligand inhibitors (bevacizumab, ramucirumab, and aflibercept), and small molecule tyrosine kinase inhibitors (TKIs; sunitinib, sorafenib, pazopanib, ponatinib, axitinib, cabozantinib, lenvatinib, regorafenib, vandetanib), which block the intracellular domain of the VEGFR.

Proteinuria is a class effect of all VEGF inhibitors. Bevacizumab, ramucirumab, aflibercept, and the small molecule antiangiogenic TKIs all produce asymptomatic proteinuria, occasionally causing nephrotic syndrome. Hypertension frequently accompanies proteinuria.

Rarely, cases of systemic drug-induced thrombotic microangiopathy (TMA) have been reported with specific antiangiogenic agents (eg, bevacizumab, sorafenib). Patients may present with microangiopathic hemolysis; renal only manifestations including acute kidney injury and/or hypertension, or proteinuria alone; or a more systemic TMA syndrome. Withdrawal of the offending agent is critical because drug-induced TMA can be fatal.

Proteasome Inhibitors

Proteasome inhibitors (PIs) are a cornerstone for the treatment of multiple myeloma (MM). First approved PI was bortezomib, and then carfilzomib and ixazomib.

There are increasing reports of TMA in association with PI exposure. It is interesting to mention that prior to the use of PIs, the incidence of TMA in patients with MM was much lower, most frequently associated with autologous stem-cell transplant and that there are no reported cases of PI-related TMA in patients with lymphoma, where PI are also used.

The morbidity and mortality of PI-related TMA are notable and for that reason, clinical vigilance is required for early detection and intervention.

OTHER BIOLOGIC AGENTS

Recombinant interferon alfa (IFNa) can cause proteinuria, which can be massive; the histology is consistent with minimal-change nephropathy or focal segmental glomerulosclerosis. Thrombotic microangiopathy is a rare complication seen mostly in patients with chronic myeloid leukemia treated with high doses of IFNa over long periods of time.

Interferon gamma has been associated with acute tubular necrosis when used for the treatment of acute lymphoblastic leukemia.

Interleukin-2

Recombinant human interleukin-2 (IL-2) can induce a relatively severe capillary leak syndrome, leading to edema, plasma volume depletion, and a reversible fall in glomerular filtration rate (GFR). It has been proposed that plasma volume depletion is responsible for the development of acute kidney failure.

the urinalysis may reveal red cells, white cells, granular casts, and modest proteinuria suggest that there may also be some direct kidney injury.

Patients with normal kidney function before treatment usually recover within the first week after discontinuing therapy.(therapy: supportive)

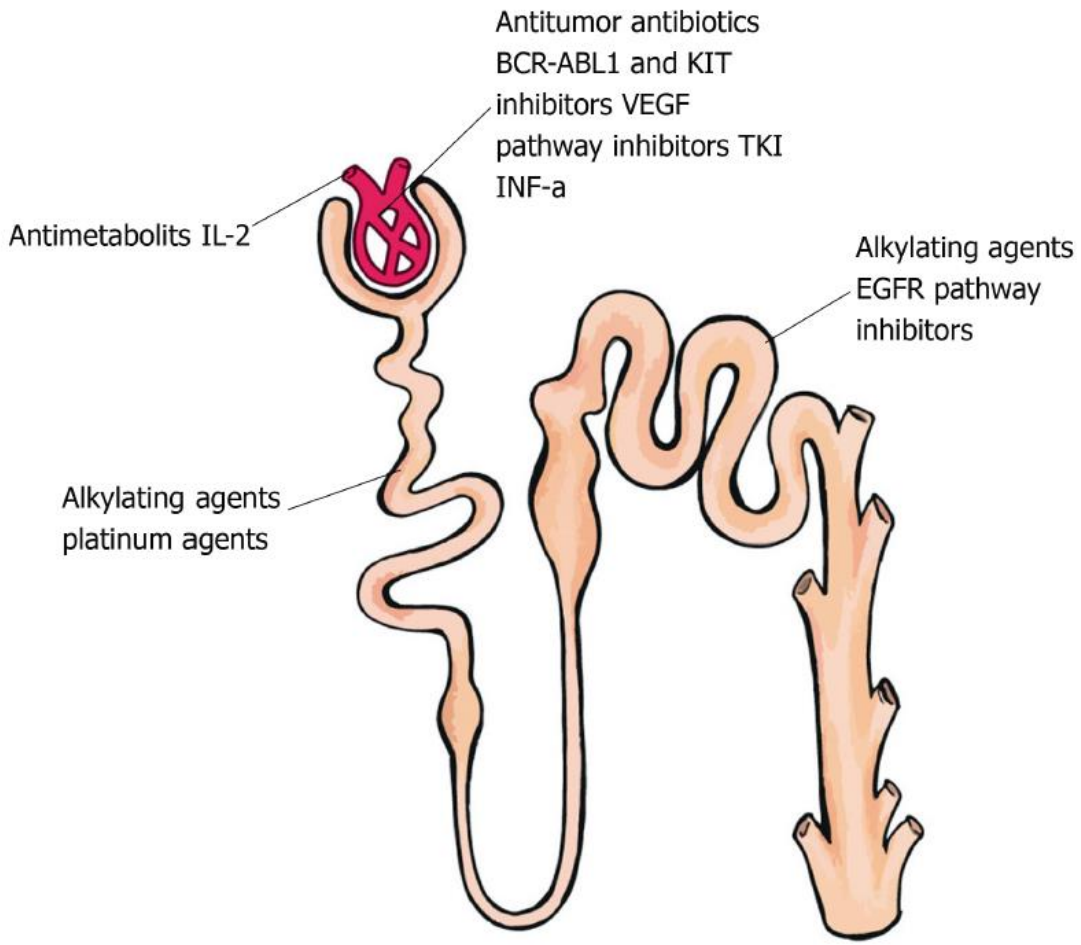

Figure 3 Chemotherapy-induced nephron specific segment injury. TKI: Tyrosine kinase inhibitors; VEGF: Vascular endothelial growth factor; IL-2: Interleukin-2; INF-a: Interferon-alpha.

Medication	Mechanism of action	Nephrotoxicity	Prevention and management recommendations
EGFR pathway inhibitors	EGFR-TKI inhibitors (erlotinib, gefitinib)	MCD Membranous nephropathy	Drug discontinuation
	anti-EGFR receptor Antibodies (cetuximab, panitumumab)	Hypomagnesemia Hypokalemia Nephrotic syndrome IgA glomerulonephritis	Drug discontinuation
Anaplastic lymphoma kinase inhibitors	Crizotinib ALK TKI inhibitor c-MET, ROS1 inhibitor	AKI (NTA and ATIN) Formation or increase of renal cysts Hypophosphatemia	Drug discontinuation
BRAF inhibitors	Inhibitors of mutant BRAF (vemurafenib, debrafenib)	Fanconi syndrome Hypophosphatemia Hyponatremia Hypokalemia AKI (NTA and ATIN)	Drug discontinuation
VEGF pathway inhibitors	VEGF-TKI inhibitors (axitinib, pazopanib, sorafenib, regorafenib, sunitinib)	FSGS/MCD (sunitinib/sorafenib) TMA (sunitinib) NTA (sunitinib/sorafenib) Hypophosphatemia, hypocalcemia, hyponatremia, hypokalemia (regorafenib)	Drug discontinuation Angiotensin-converting enzyme inhibitor
	Anti- VEGF receptor antibodies Bevacizumab: mAb against VEGFA. Aflibercept: Recombinant fusion protein (VEGF trap) Ramucirumab: mAb against VEGFR2	TMA IgA nephropathy ANCA glomerulonephritis Diabetic nephropathy FSGS/MCD Membranous nephropathy	Drug discontinuation Angiotensin-converting enzyme inhibitor
Bcr-abl TKIs (Bcr-abl TKI)	1st generation: Nilotinib, imatinib ATP-competitive TKI Src family kinases inhibition	Hypophosphatemia Reversible decrease in GFR AKI (TLS) NTA (imatinib)	Monitoring of renal function Dose reduction when decrease GFR
	2nd generation: dasatinib Platelet-derived growth factor receptor Tyrosine kinase receptor KIT (CD117) VEGF inhibition Ibrutinib	Proteinuria, nephrotic syndrome: (dasatinib) NTA (ibrutinib)	Dose reduction o drug discontinuation Change 1st generation Bcr-abl tyrosine kinase inhibitors

EGFR, epidermal growth factor receptor, TKI: EGFR-tyrosine kinase inhibitors; 2. BRAF, encoding gene human protein B-Raf; VEGF, vascular endothelial growth factor; MCD, minimal change disease; FSGF, focal segmental glomerulosclerosis; AKI, acute kidney injury; ATN, acute tubular necrosis; NTIA, acute tubulointerstitial nephritis; TMA, thrombotic microangiopathy; CKD, chronic kidney injury; TLS, tumor lysis syndrome.

Table 3. Cancer immunotherapies and nephrotoxicity

Medication	Nephrotoxicity	Mechanism of nephrotoxicity	Prevention and management recommendations
IFN	MCD/FSGS TMA	Direct effects of IFN on the podocyte Indirect effects via altered cytokine milieu Damage microvascular endothelial cells by inducing apoptosis in a dose-dependent manner	Drug discontinuation Steroids (MCD/FSGS)
Interleukin-2	Hemodynamic AKI ATI	Capillary leak syndrome leading to AKI	Volume filling
CAR-T	Hemodynamic AKI ATI TLS	CRS	Previous chemotherapy/ steroids Supportive treatment Anti-IL-6: Tocilizumab
Immune checkpoint inhibitors (CTLA-4 inhibitors, PD-1 inhibitors, PD-L1 inhibitors)	ATIN ATI Lupus-like glomerulonephritis Podocytopathies Necrotizing glomerulonephritis and vasculitis C3 glomerulonephritis TMA	Formation of new or reactivated T cells against tumor antigens that cross-react with kidney antigens Loss of tolerance with reactivation of drug-specific T cell induced by ICI Increase in proinflammatory cytokines in kidney tissue Generation of autoantibodies against kidney tissues	CPI withdrawal Steroids

MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; TMA, thrombotic microangiopathy; ATI, acute tubular injury; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed death protein 1; PD-L1, programmed death-ligand 1.