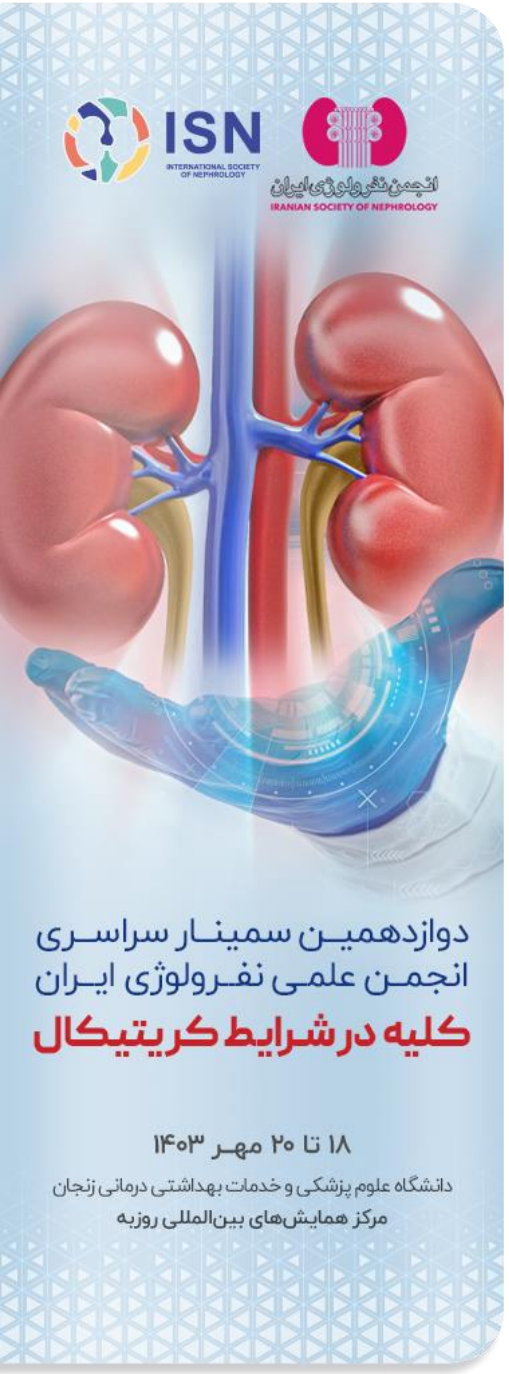

AKI INDUCED BY CHEMOTHERAPY AND CANCER IMMUNOTHERAPY

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Introduction

- Cancer is one of the leading causes of death and increased morbidity in the world.
- The kidney is an important elimination pathway for many antineoplastic drugs and their metabolites (glomerular filtration, tubular secretion).
- Renal function impairment is one of the major limitations of cancer treatment and increases mortality and morbidity in patients with cancer.
- Patients with cancer who develop AKI during oncologic treatments and patients with CKD who develop cancer are frequently medicated with suboptimal therapeutic choices because of the lack of randomized clinical trials in population with impaired renal function

Conventional Chemotherapy

- Conventional chemotherapy has been classically associated with AKI; caused primarily by acute tubular toxicity, acute tubulointerstitial nephritis (ATIN), and different glomerulonephritis.
- It is frequently related with drug dosage and treatment duration.

Platinum Compounds (Cisplatin, Carboplatin, Oxaliplatin)

- 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 hypomagnesemia, nephrogenic diabetes insipidus, proximal tubulopathy, and less frequently with thrombotic microangiopathy.
- 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.

Platinum Compounds (Cisplatin, Carboplatin, Oxaliplatin)

- 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 (like nonsteroidal anti-inflammatory drugs NSAIDS, iodinated contrast).

Ifosfamide

- Alkylating drug
- Combined with cisplatin: sarcomas, testicular tumors, and some refractory lymphomas.
- Its renal toxicity has been associated with proximal tubular dysfunction (Fanconi Syndrome) and AKI, 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. (IFTA reported)

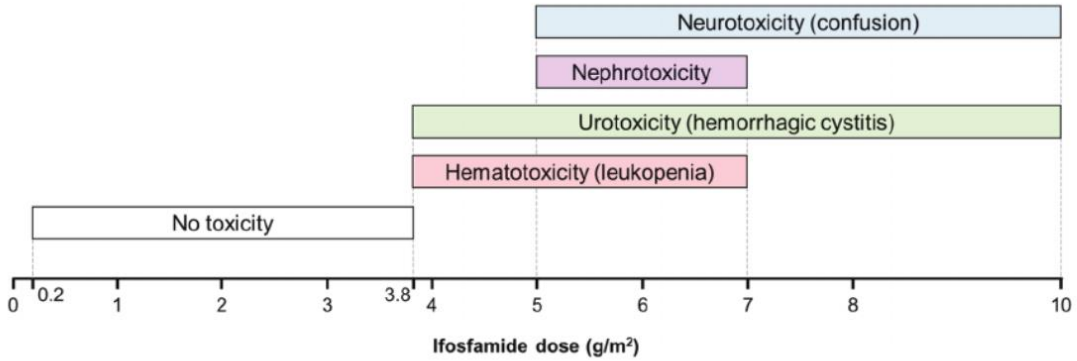
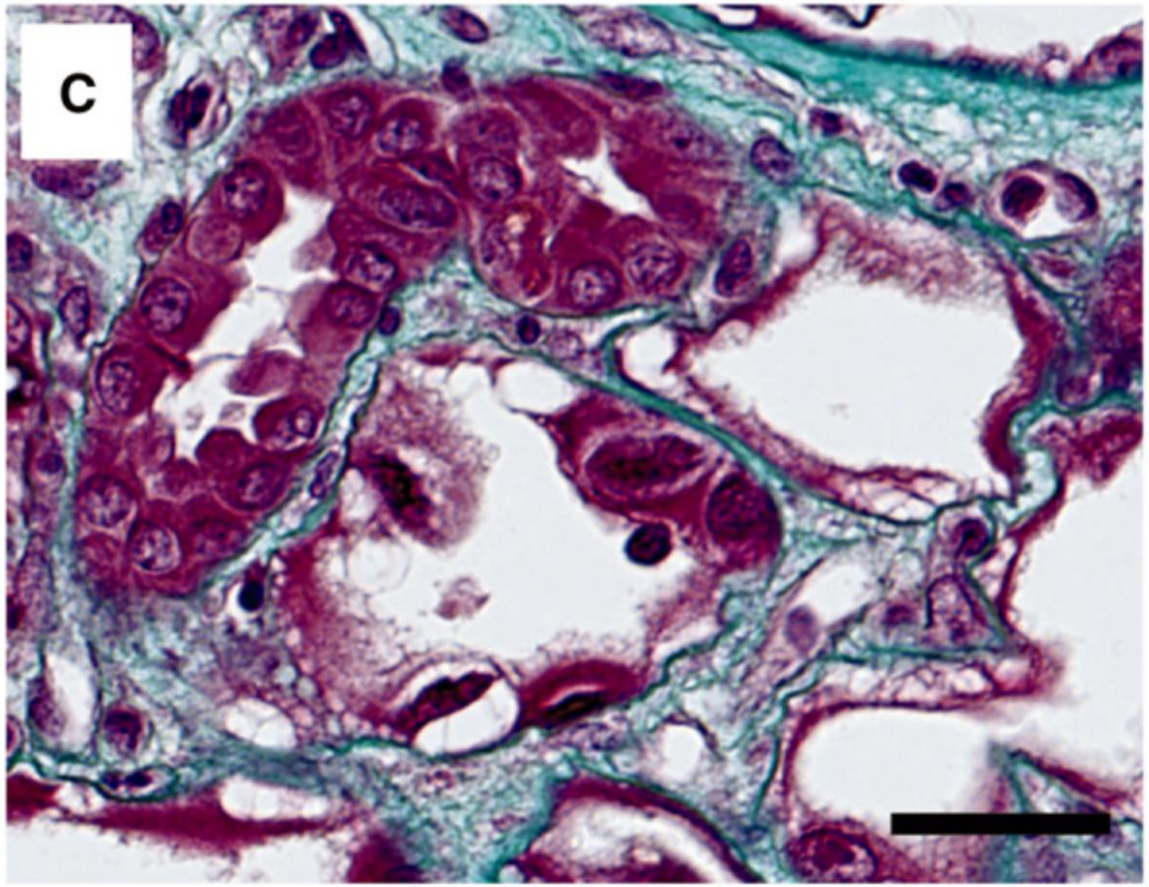


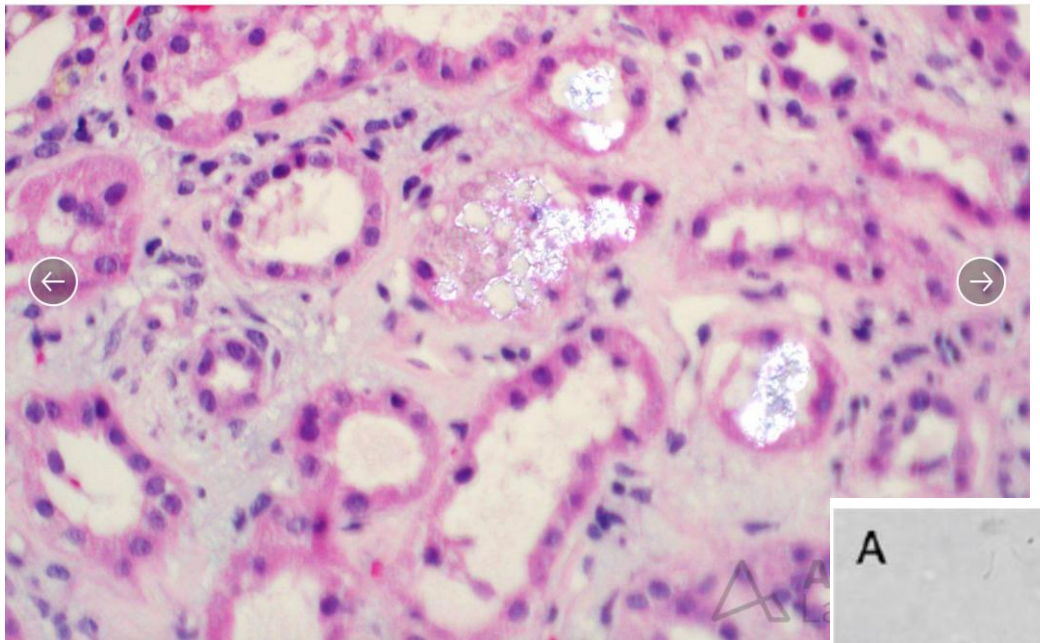
Figure 3. Toxic effects of ifosfamide according to the administered dose. Observation of the toxic effects associated with ifosfamide administered at different doses, based on the results of the clinical trial conducted by Cohen et al. In 1975 [43].



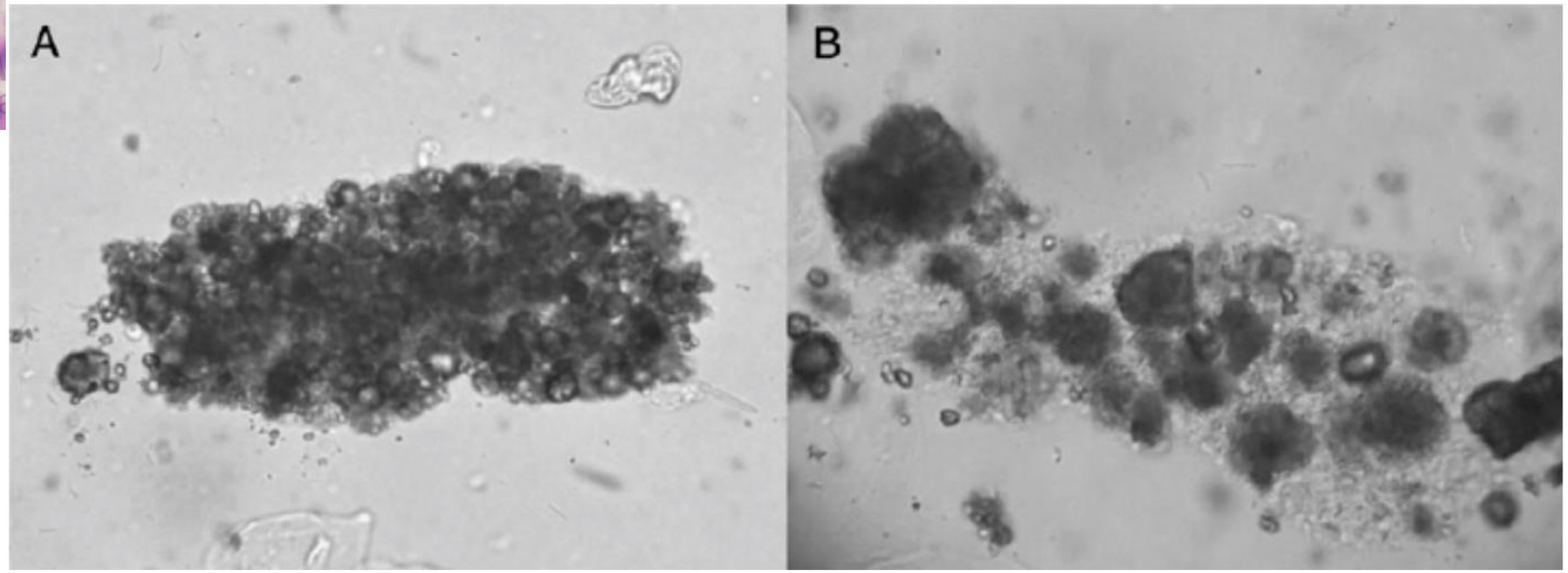
Expert Review of Anticancer Therapy 2023

Methotrexate

- Methotrexate precipitation and metabolites within tubular lumen lead to AKI and crystalline nephropathy.
- After AKI occurs, the excretion of the drug is reduced and the patient can develop systemic toxicity.
- Several strategies can be used when AKI and severe systemic toxicities developed:
- high-dose of leucovorin therapy (a folate compound),
- prolonged hemodialysis (daily for several days, to avoid rebound)
- glucarpidase (an enzyme that inactivates the drug)



MTX crystals



Methotrexate crystalline-induced kidney injury. (A) Urine sediment shows free and clumped methotrexate crystals under light microscopy (×400) and a (B) methotrexate crystalline cast (× 400).

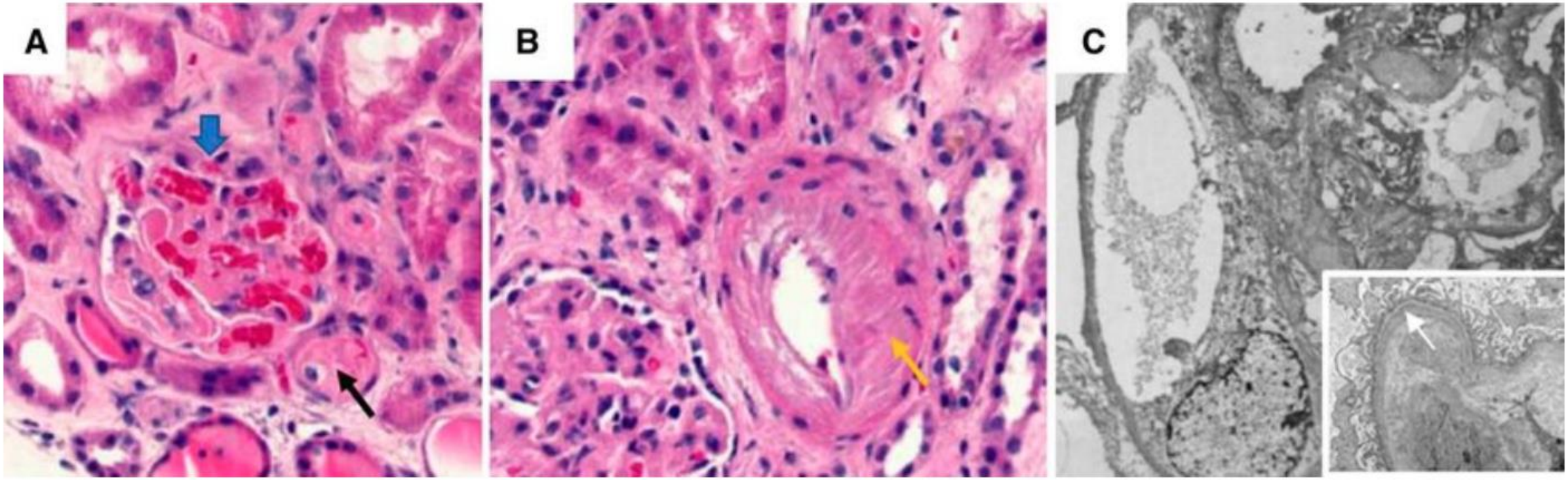
Pemetrexed

- methotrexate analog
- It has been associated with AKI, proximal tubulopathy, and nephrogenic diabetes insipidus.
- Renal histology reveals ATN with mild-to- moderate interstitial fibrosis and, in a minority of cases, mild interstitial inflammation.
- Pemetrexed is contraindicated when the estimated creatinine clearance is <45 mL/min because of fatal toxicities in patients with renal impairment.
- In that line, innovative interventions as leucovorin therapy, used for methotrexate toxicity, are needed to allow a safe treatment

Gemcitabine

- Thrombotic microangioapthy (TMA) (characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end-organ damage) is a rare complication related with gemcitabine with a high mortality rate.
- In the largest case series of TMA related to gemcitabine: new-onset or exacerbated HTN and edema as early signs of TMA, suggesting that in front of these clinical symptoms close monitoring may be useful.

Some case reports suggest that complement inhibition with eculizumab could be a reasonable therapy when plasmapheresis failed in patients with gemcitabine-associated TMA.



Histologic findings in a patient with gemcitabine-associated thrombotic microangiopathy
(A) a glomerulus (wide blue arrow) with intraglomerular thrombi, mesangiolysis, entrapped intraglomerular thrombi, and a vessel (black arrow) with luminal occlusion and intimal thrombi,
(B) vessel (yellow arrow) with intimal edema and sclerosis.
(C) Electron microscopy showing mesangiolysis, diffuse endothelial swelling, and duplication of the glomerular basement membrane with expansion of the lamina rara interna (white arrow).

KIDNEY360 4: 409–422, March, 2023

Mitomycin C

- Mitomycin C is also related with dose-dependent TMA.
- Drug discontinuation and supportive care are indicated in that case, as plasmapheresis is ineffective.

Gemcitabine, mitomycin C, and platinum compounds were categorized "Type I" cancer drug TMA

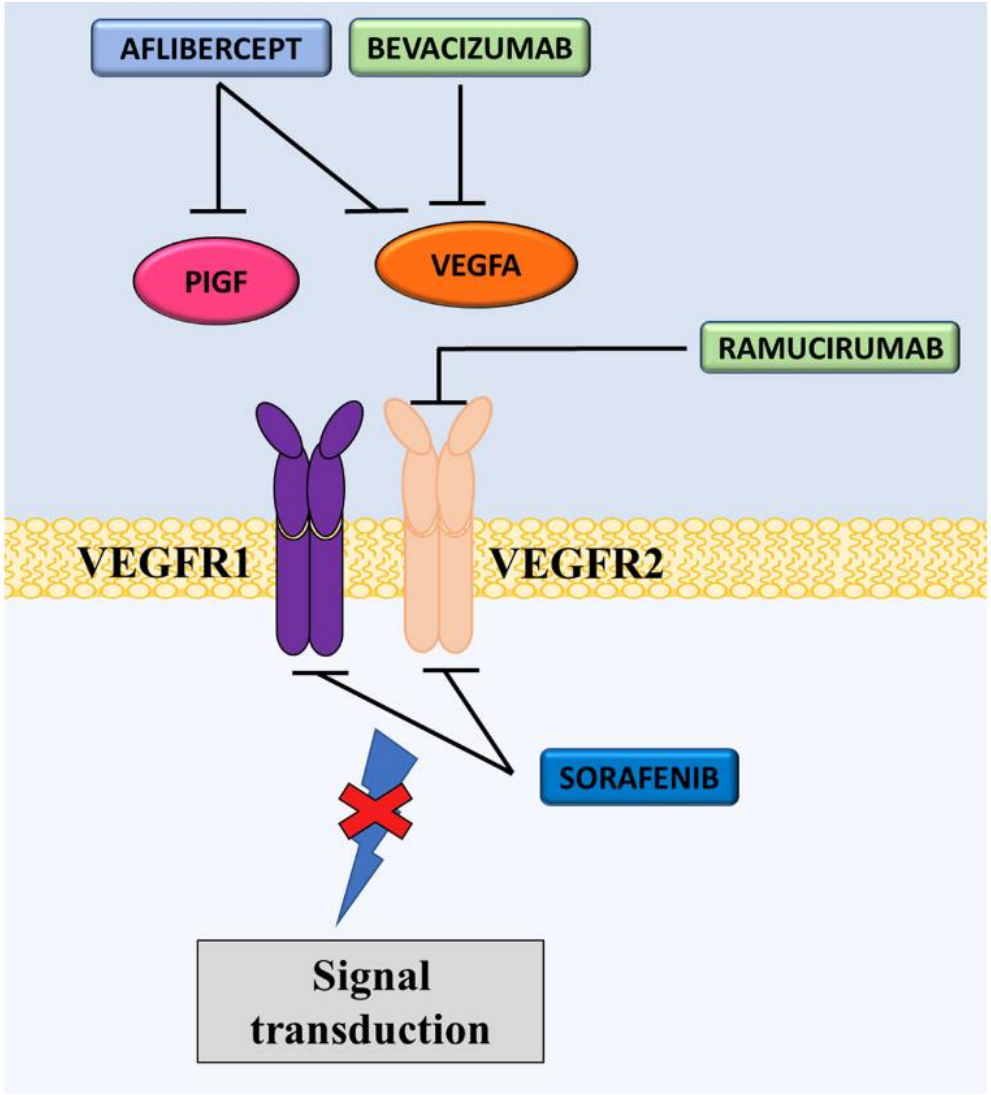
Anti-vascular endothelial growth factor (VEGF) agents are cathegorized "Type II" cancer drug TMA, on the basis of their different mechanisms of kidney injury and outcomes

Types of cancer drugs TMA

- 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.

Target Cancer Agents

- The most commonly used cancer therapies are targeted to:
- proteasome
- vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR)
- epidermal growth factor receptor (EGFR)
- human epidermal growth factor receptor-2 (HER2)
- v-Raf murine sarcoma viral oncogene homologue B (BRAF)
- anaplastic lymphoma kinase (ALK)
- mammalian target of rapamycin (mTOR)



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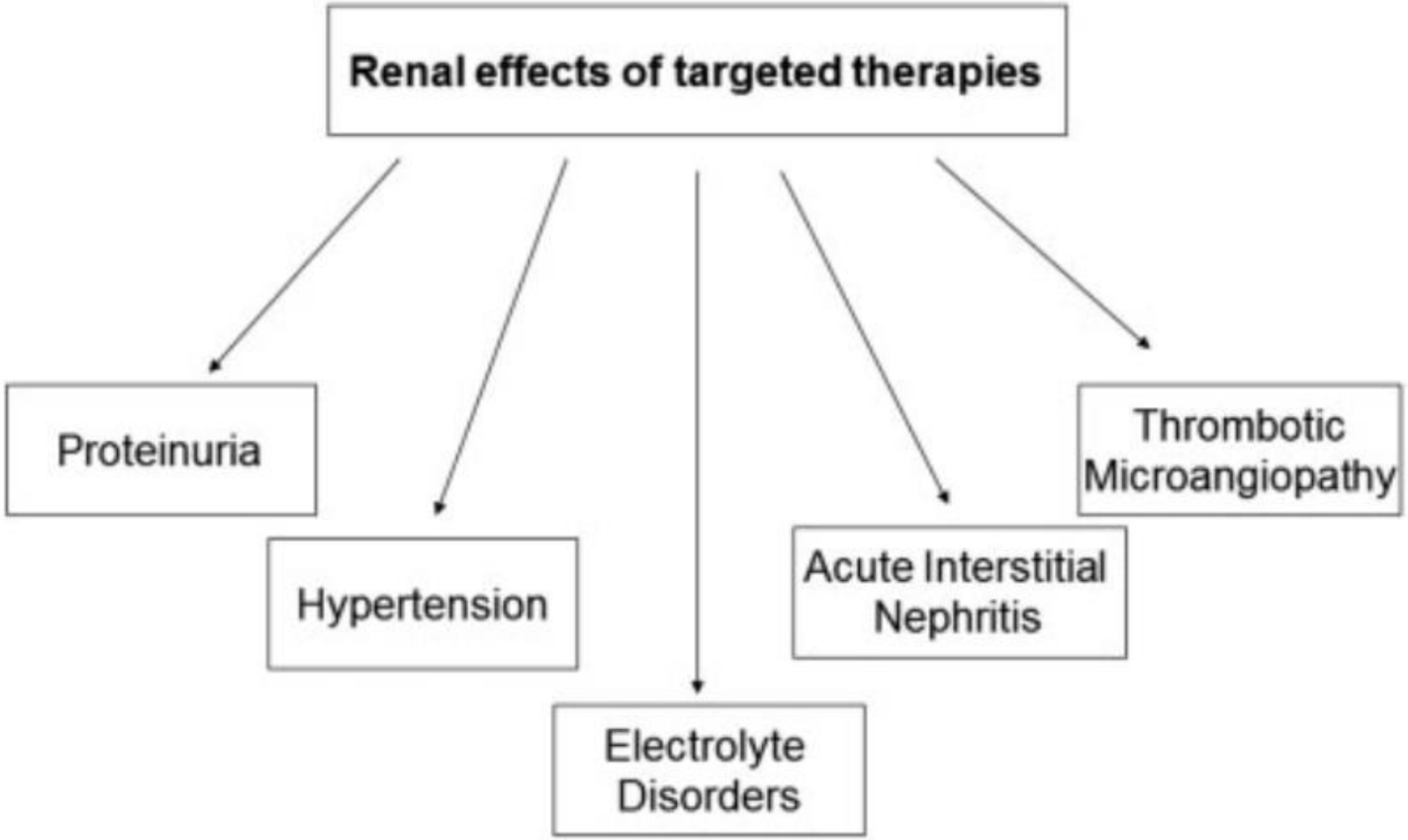


FIGURE 2: Renal effects of targeted therapies.

Nephrol Dial Transplant (2017)

Proteasome Inhibitors

- Proteasome inhibitors (PIs) are a cornerstone for the treatment of multiple myeloma.
- First approved PI was bortezomib, and then carfilzomib and ixazomib.
- There are increasing reports of TMA in association with PI exposure.
- There are no reported cases of PI-related TMA in patients with lymphoma, where PI are also used.
- Thus, MM itself could be a risk factor for PI-induced TMA.
- Kidney and supportive treatment, including renal replacement therapies and blood transfusions, is needed, as well as a cessation of PI and any other offending agent.
- TMA seems to be more frequent in patients on carfilzomib than in those on bortezomib according to the literature.

Anti-VEGF

- Bevacizumab and aflibercept are increasingly applied to treat malignancies like metastatic or recurrent colorectal, non-small cell lung, breast, and renal cell cancers and ramucirumab has been approved as a second line therapy for gastric, non-small-cell lung, and metastatic colorectal cancers.
- Despite their mechanisms of action are not the same, the three drugs inhibit endothelial cell proliferation and vessel development and can cause HTN, asymptomatic albuminuria, nephrotic syndrome, and TMA.
- VEGF is mainly expressed in podocytes and required to maintain the integrity of glomerular endothelial function and glomerular filtration barrier.

Anti-VEGF (Cont.…)

- The less severe renal adverse event associated with anti-VEGF is HTN, which appears in 16%–43% of patients.
- Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARB) are the first-line therapy and calcium channel blockers are the second choice.
- Diuretic agents can also be added. Normally, blood pressure can be controlled and it is not necessary to stop the cancer treatment.

Anti-VEGF (Cont…)

- All degree of proteinuria is more common in patients on aflibercept than in those on bevacizumab (33.9% vs. 13.3%) and it is associated to the disruption of the glomerular filtration barrier.
- Treatment can be continued in most cases involving non-nephrotic-range proteinuria, and HTN and proteinuria can be aggressively managed with ACEIs or ARBs.
- Risk factors for the development of proteinuria are base- line elevated systolic blood pressure, number of cycles of anti-VEGF drug, and previous use of calcium channel blockers.
- If possible, kidney biopsy is recommended when proteinuria appears, but even more when it is over 3 g per day or associated to AKI, since histological findings could influence prognosis and treatment options.

Anti-VEGF (Cont…)

- Anti-VEGF therapies have been related with minimal change disease and focal segmental glomerulosclerosis (FSGS), but the most common histologic pattern is TMA.
- Anti-VEGF-associated TMA, as well as nephrotic range proteinuria, are considered a reason to discontinue the culprit drug.
- Renal response to discontinuation of the of offending agent is normally good with no need of other specific treatment.
- Recently, some case series of bevacizumab-associated TMA treated with eculizumab have been reported, suggesting that complement blockade should be an option for patients without response to the classical management.

BRAF (v-raf murine sarcoma viral oncogene homolog B1) **Inhibitors**

The BRAF inhibitors vemurafenib, dabrafenib and encorafenib are used in the treatment of patients with BRAF-mutant melanoma.

Medication	Mechanism of action	Nephrotoxicity	Prevention and management recommendations
BRAF inhibitors	Inhibitors of mutant BRAF (vemurafenib, debrafenib)	Fanconi syndrome Hypophosphatemia Hyponatremia Hypokalemia AKI (NTA and ATIN)	Drug discontinuation

TKIs (Axitinib, Pazopanib, Sorafenib, Regorafenib, Sunitinib)

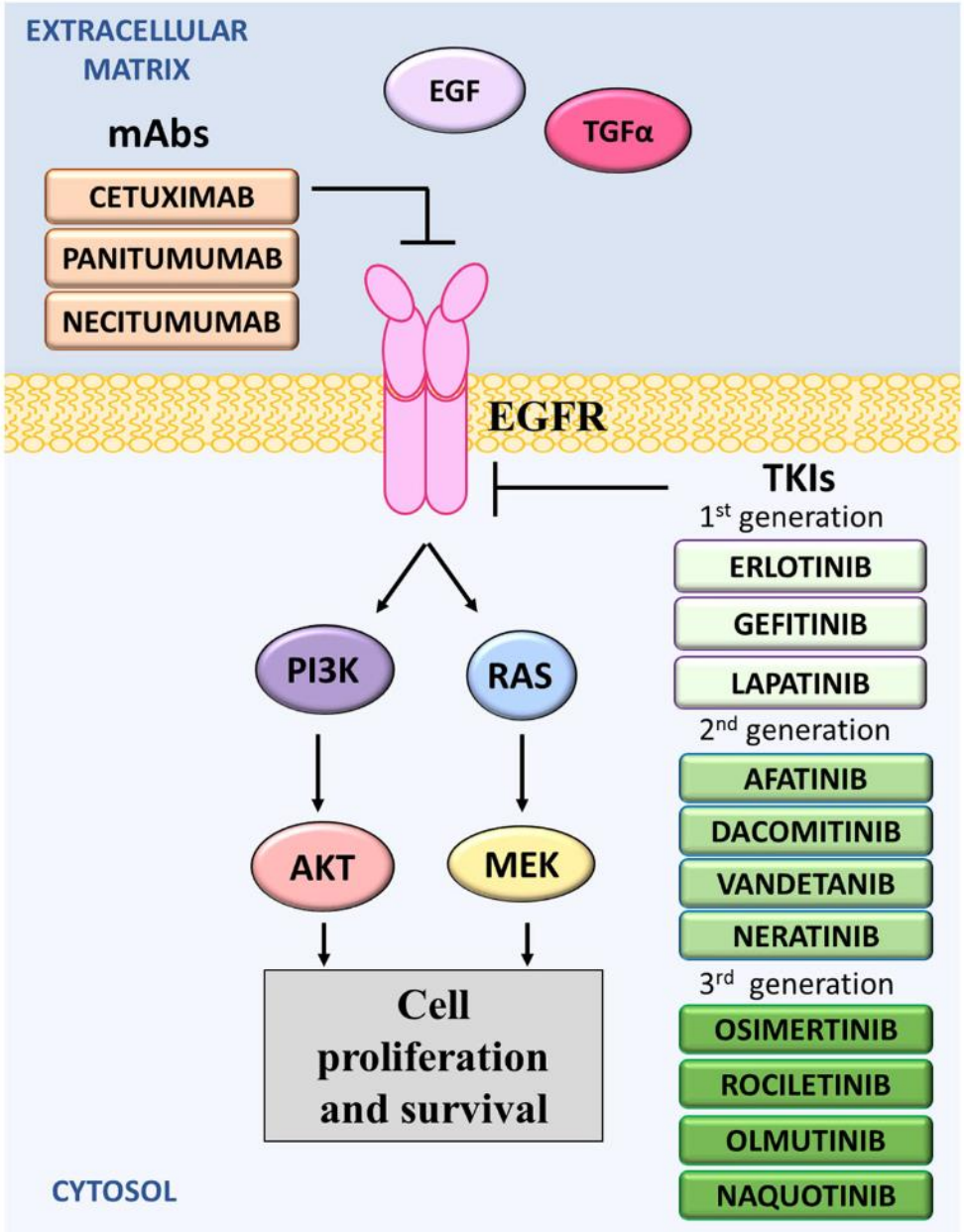
- Decreased GFR has been reported during therapy with axitinib, sunitinib, and sorafenib, although renal failure is rare.
- TKIs are also related with TMA.
- In particular, sunitinib in a case report of 5 patients has been associated with AKI, eosinophilia, and/or nephrotic syndrome, and/or TMA.
- Regorafenib has been associated with several electrolyte abnormalities, including hypophosphatemia, hypocalcemia, hyponatremia, and hypokalemia.

Bcr-Abl TKIs

The first-line therapy for most patients with chronic myelogenous leukemia (CML)

Medication	Mechanism of action	Nephrotoxicity	Prevention and management recommendations
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

Nephron 2023;147:65–77



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EGFR Inhibitors (Cetuximab, Erlotinib, Gefitinib, Panitumumab)

EGFR inhibitors have been associated with electrolyte disorders; mainly hypomagnesemia; but also hypophosphatemia, and hypokalemia. Increased renal magnesium has been found in 37% of patients, which resolves with therapy discontinuation. Cetuximab has also been associated with a single case of IgA glomerulonephritis and nephrotic syndrome.

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

Nephron 2023;147:65–77

Cancer Immunotherapies

- Outcomes in advanced neoplasia’s have dramatically changed over the last decades. The use of drugs that modulate the immune response instead of direct tumor targeting plays an important role in this improvement in Oncology.
- However, the goal of modifying immune response has been linked to renal-related adverse effects that could limit the potential use of these treatments.

Interferons

- IFNs have been related to nephrotic syndrome and AKI secondary to minimal change disease and FSGS.
- Renal response to drug discontinuation is favorable in published series and steroids can also be used. Black race and some APOL1 gene variants have been identified as risk factors for the development of nephrotic syndrome under IFN treatment.

Interleukin-2

- The main toxicity of IL2 is a capillary leak syndrome in relation to an increased level of circulating cytokines.
- This could drive to a hypovolemic/pre-renal AKI within 24–48 h after the drug infusion.
- Generally, AKI improves after IL-2 discontinuation and supportive care.
- However, an acute tubular injury could be present if ischemia was important and renal function recovery could be partial or delayed.

Chimeric Antigen Receptor T-Cell (CAR-T)

- The main adverse effect of CAR-T cells therapy is cytokine release syndrome (CRS) in the onset of immune activation, that could drive to hemodynamic AKI or acute tubular injury in approximately 20% of patients.
- The rapid onset of tumor destroy by CAR-T cells could also promote a TLS and secondary renal injury.
- Acute tubular necrosis is related to a longer hospital stay and a higher 60 days mortality.
- Previous chemotherapy and steroids are recommended with the aim to reduce tumor size and to minimize CRS in patients who will be under CAR-T cells therapy for preventing AKI.
- Admission in critical care units for supportive treatment is justified. Moreover, interleukin-6 receptor blockers (tocilizumab), are useful to reduce systemic inflammation and, consequently, are useful in preventing the development and in the management of AKI related to CAR-T cells therapies.

Table 4. Chimeric antigen receptor T cell–associated nephrotoxicity

Potential Nephrotoxicity
AKI
Prerenal AKI/acute tubular injury
Cytokine release syndrome with capillary leak and hypotension
Hemophagocytic lymphohistiocytosis with inflammation
Acute cardiac dysfunction with reduced cardiac output and hypotension
Intravascular volume depletion from fever, N/V, and diarrhea
Tumor lysis syndrome
Electrolyte disorders
Hypokalemia, hypophosphatemia, and hyponatremia
Prevention/treatment of toxicity
Chemotherapy to reduce tumor burden
Corticosteroids to reduce inflammatory response
Supportive care for hypotension with vasopressors, iv fluids, and oxygen
IL-6 blockade with tocilizumab for cytokine release syndrome and hemophagocytic lymphohistiocytosis

N/V, nausea and vomiting.

J Am Soc Nephrol 29: 2039–2052, 2018

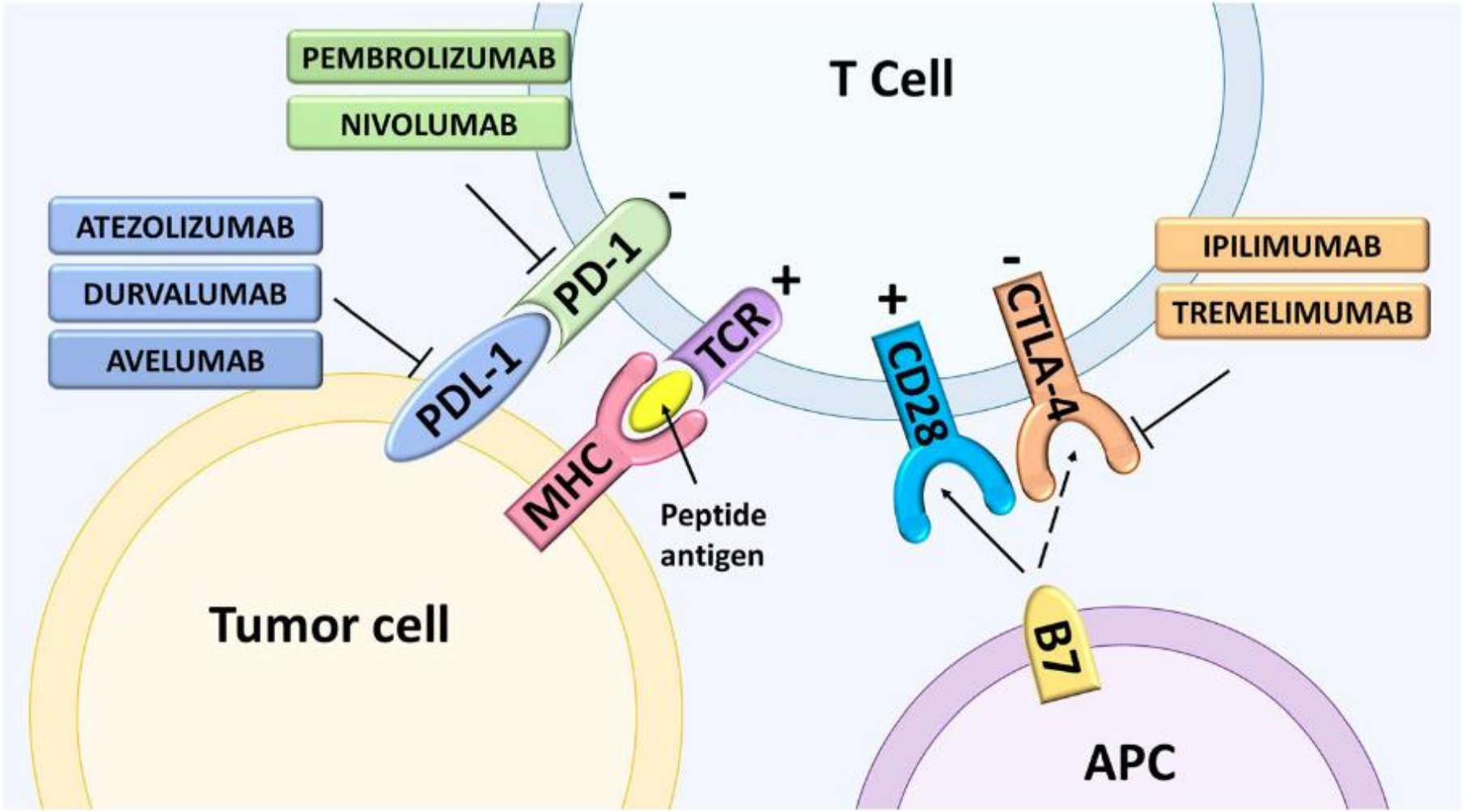
Cytokine Release Syndrome (CRS)

- Cytokine release syndrome (CRS) is a systemic inflammatory response that occurs on activation of CAR-T cells and destruction of tumor cells.
- In this setting, IL-6, IL-10, and IFN-γ as well as inflammatory markers C-reactive protein and ferritin are produced.
- This syndrome manifests with high fever, myalgias, and tachycardia within 1–14 days of CAR T cell infusion and can progress to vasodilatory shock and capillary leak with multiorgan failure.
- A subset of patients with CRS also developed hepatosplenomegaly and liver dysfunction, increased ferritin levels, and decreased fibrinogen levels with coagulopathy.

Immune Checkpoint Inhibitors (CTLA-4 Inhibitors, PD-1 Inhibitors, PD-L1 Inhibitors)

- Since CPI mechanisms are not selective, these drugs cause diverse autoimmune phenomena known as immune-related adverse events.
- AKI incidence has been increasing to 13–29%.
- Biopsy-proven or clinically CPI-related AKI has been only found in 2%–3%.
- The development of AKI has been identified as a risk factor for mortality as well as an absence of renal recovery after an AKI episode.

A special characteristic of AKI-related to CPI is that it occurs from some weeks to many months after treatment initiation.

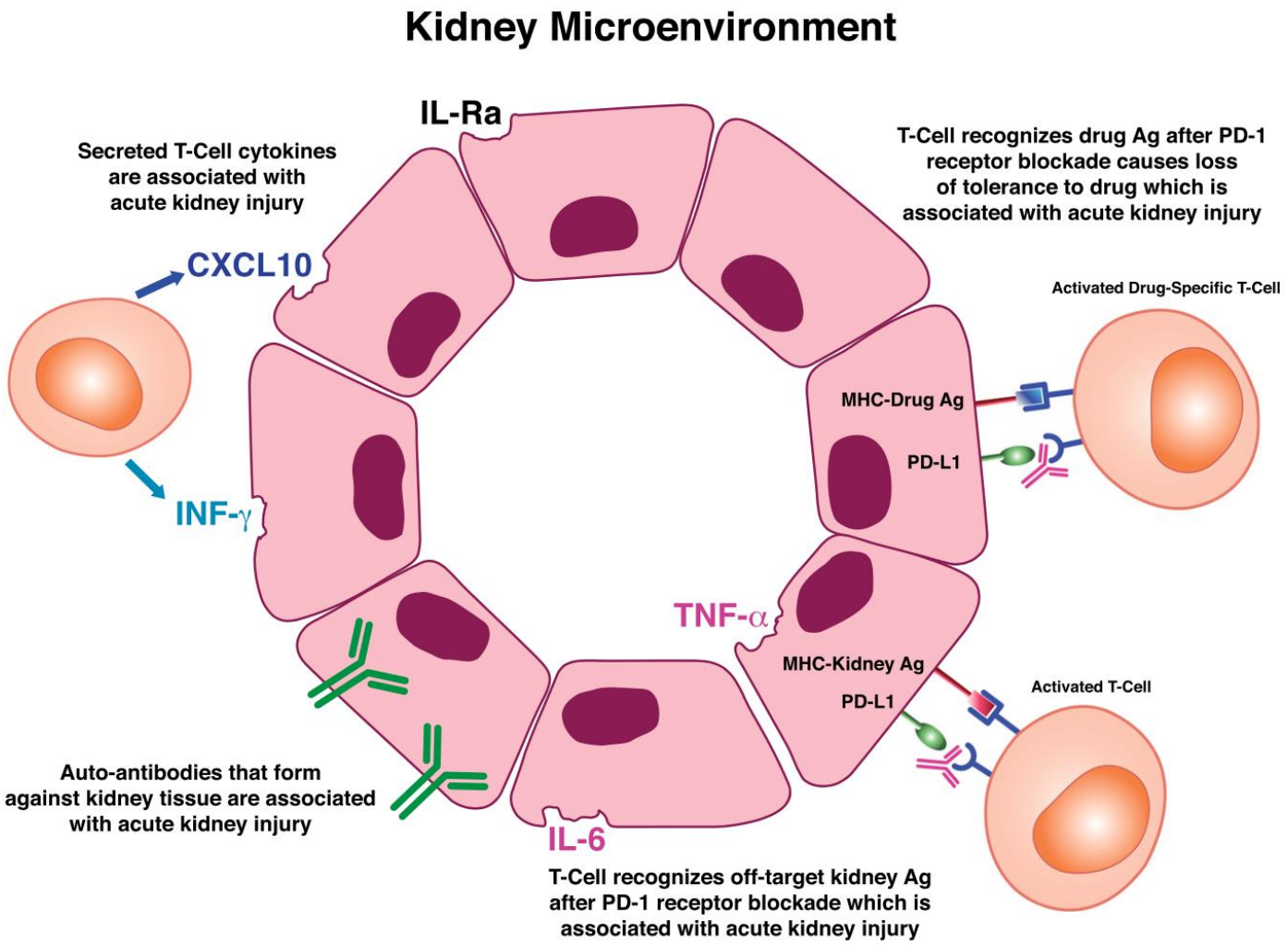


Seebacher et al. Journal of Experimental & Clinical Cancer Research (2019) 38:156

Immune-related adverse events (IrAEs)

- An irAE is defined as an inflammatory side effect attributed to a nonspecific increase in immune response with the use of CPIs.
- Authors have reported irAEs in almost every system in the body, with the most common involving the gastrointestinal tract (liver and colon), skin, endocrine system, and lungs, whereas hematological, neurological, cardiac, and renal irAEs are much less frequent.
- Although the kidneys are less involved, nephrotoxicity occurs in up to 2% to 5%, with a higher risk with combination ICIs. While initial studies noted a small incidence of AKI (2–3%), recent data suggest a higher incidence rate closer to 13–29% with ICI.

Proposed mechanisms of irAEs



- Autoreactive T cells
- Checkpoint receptors expressed on nontumor tissue
- Cross-presentation of antigens
- Loss of tolerance leading to reactivation of latent antibodies
- T-reg depletion
- Cytokines (Proinflammatory cytokines such as IL-17)
- Autoantibody formation
- A genetic predisposition for irAE development
- Environmental factors

Risk factors for AKI related to CPI

- Patient age
- Impaired baseline renal function
- Concomitant use of proton pomp inhibitors
- Combination of more than one CPI
- The presence of previous immune-related adverse events

The most frequent renal histologic pattern in patients with biopsy-proven CPI-related AKI

- acute tubulointerstitial nephritis (ATIN)
- glomerular lesions have also been described, such as renal vasculitis, podo-cytopathies, and C3 glomerulonephritis.
- When compared to classical ATIN, CPI-related ATIN presented with lower creatinine at diagnosis, higher urinary leucocyte counts, and time from initiation of the culprit drug to ATIN diagnosis was longer in patients with CPI-related ATIN than in those with classical ATIN.

Diagnosis and management of ICI-Related AKI

- The National Comprehensive Cancer Network (NCCN) does not recommend kidney biopsy unless Grade 2-3 or higher AKI develops, and the American Society of Oncology (ASCO) recommends proceeding with corticosteroids without kidney biopsy.
- There are select situations such as a solitary kidney, need for ongoing anticoagulation, or patient refusal where kidney biopsy cannot be performed safely.

Table 4. American society of clinical oncology grading and treatment of renal immune-related adverse events (adapted from [66]).

	Grade 1	Grade 2	Grade 3	Grade 4
Diagnosis	Creatinine level increase of >0.3 mg/dL.; creatinine 1.5–2× above baseline	Creatinine 2–3× above baseline	Creatinine > 3 × baseline or > 4.0 mg/dL.; hospitalization indicated	Life-threatening consequences; dialysis indicated; creatinine 6× above baseline
Management *	Consider temporarily holding ICI	Hold ICI temporarily. Administer corticosteroids (0.5–1 mg/kg/day prednisone equivalents). If worsening or no improvement after 1 week, increase to 1–2 mg/kg/day and permanently discontinue ICI.	Permanently discontinue ICI Administer corticosteroids (initial dose of 1–2 mg/kg/d prednisone or equivalent). If elevations persist or worsen, consider additional immunosuppression (e.g., infliximab, azathioprine, cyclophosphamide (monthly), cyclosporine, and mycophenolate).	

* Non-specific management include exclusion of potential alternative etiologies, fluid status optimization and nephroprotective therapy.

Cells **2022**

Other Therapies

Bisphosphonates

- Kidney damage is related to dose and infusion time and both pamidronate and zoledronate could cause acute tubular necrosis and nephrotic syndrome with FSGS histologic pattern.

mTOR Inhibitors

- The main renal complication of everolimus and sirolimus is proteinuria, reported in 3%–36% of patients.
- Sirolimus has also been associated with nephrotic syndrome in 2% of cases, with an FSGS and membranoproliferative histologic pattern.

Other Therapies

Calcineurin Inhibitors

- CNI are also used in allogenic hematopoietic stem-cell transplantation (HSCT) and their use may be associated with AKI.
- Major renal effects of CNI are renal vessel constriction, endothelial damage, and tubular toxicity.
- However, cyclosporine A and tacrolimus can also cause CNI-related TMA, that sometimes is limited to kidney but can also have peripheral expression that sometimes requires supportive care in recent HSCT recipients.

Table 1. Risk factors for chemotherapy-induced nephrotoxicity

- Tumor-related kidney effects
  - direct renal involvement
    - myeloma-related kidney injury
    - renal infiltration (lymphoma and leukemia)
    - urinary obstruction
    - neoplasia-associated glomerulopathies
  - indirect renal involvement
    - true volume depletion (N/V, diarrhea, and overdiuresis)
    - effective volume depletion (cardiomyopathy, malignant ascites, and pleural effusions)
    - metabolic effects (hyperuricemia and hypercalcemia)
- Innate drug toxicity
  - high-dose drug exposure and prolonged course of therapy
  - insoluble drug or metabolite form crystals within intratubular lumens
  - potent direct nephrotoxic effects of the drug or toxin
  - drug combinations enhance nephrotoxicity
    - NSAIDs, aminoglycosides, and radiocontrast
- Patient factors
  - older age
  - underlying AKI or CKD
  - immune response genes
    - increased allergic reactions to drugs
  - pharmacogenetics favoring drug/toxin toxicity
    - gene mutations in hepatic and renal CYP450 enzyme systems
    - gene mutations in transport proteins and renal transporters
- Renal drug handling
  - high blood (and drug) delivery rate to the kidneys
  - proximal tubular uptake of toxins
    - apical tubular uptake by endocytosis or another pathway
    - basolateral tubular transport through OAT and OCT pathways
  - relatively hypoxic renal environment
  - high metabolic rate of tubular cells in the loop of Henle
  - increased drug/toxin concentration in renal medulla and interstitium
  - biotransformation of substances to ROS causing oxidative stress

FINALLY

- Onco-nephrology has emerged as a new specialized therapeutic perspective for cancer patients.
- Despite the improvement of patients survival resulting from the use of conventional and molecularly targeted agents, several therapeutic complications due to nephrotoxic effects of these drugs have been reported.
- Given the background, it is important to know the possible adverse events related to these therapies, allowing early diagnosis of these effects, avoiding further issues due to this treatment.
- It is important to highlight that the approach in patients affected by nephrotoxicity due to anti-cancer drugs include, close monitoring, proper hydration and dose reduction, with suspension of the agent use if necessary.


Thank You
for
listening