Nephrotoxicity of targeted molecular agents and immunotherapy

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- Cancer : an important cause of death worldwide and associated with significant morbidity related to the underlying disease itself as well as side effects of chemotherapy.
- Conventional chemotherapy drugs :

  first-line drugs for the treatment of several malignancies,

  but they cause renal toxicity, which is harmful due to the action of chemicals.
- molecularly targeted agents :

✓ new cancer drugs

✓ more specific against cancer cells

✓ highly effective against several previously untreatable malignancies,

but also cause nephrotoxicity, which limits the effectiveness of treatment and affects their quality of life and overall survival.

- A variety of kidney complications can occur among cancer patients with malignancy

  kidney paraneoplastic manifestations,

  the need for nephrectomy and

  urinary tract obstruction or

its treatment : Nephrotoxicity effects of chemotherapy:

AKI, due to acute toxic tubular necrosis, TMA and crystalline nephropathy, proteinuria/nephrotic syndrome caused by TMA and glomerulopathies and tubulopathies caused by Electrolyte and acid-base disturbances and

CKD due to glomerulopathy or interstitial nephritis [or internal renal damage associated with the patient's previous risk factors such as female gender, decreased muscle mass and decreased body water - mainly related to older age, hypertension, Diabetes, congestive heart failure, cirrhosis, liver failure, hyperbilirubinemia and hypoalbuminemia.

- Kidney-related risk factors are nephrosis, previous kidney damage, nephrotic syndrome, and hydroelectrolytic disorder, which can result in vomiting, diarrhea, and the use of diuretics.

Renal effects of anticancer drugs

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

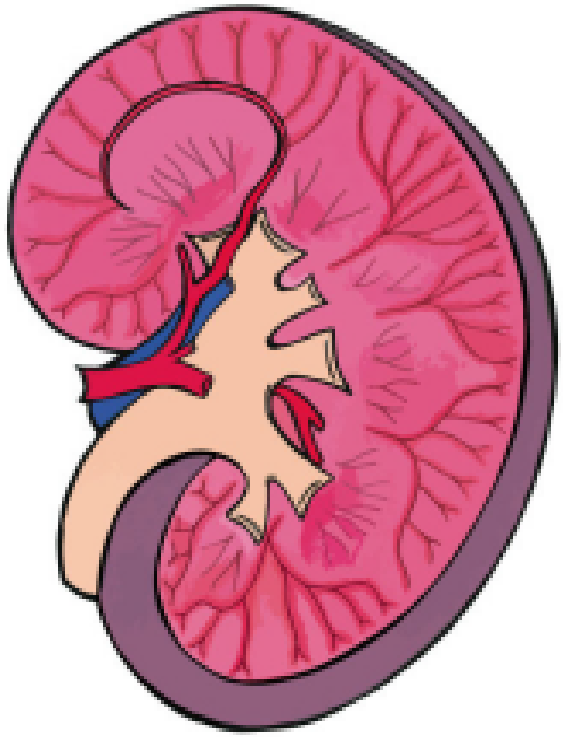


Figure 1 - Renal effects of anticancer drugs

AKI:Acute Kidney Injury ; CKD:Chronic Kidney Disease ; SIADH:Syndrome of Inappropriate AntiDiuretic Hormone secretion ; TMA:Thrombotic MicroAngiopathy

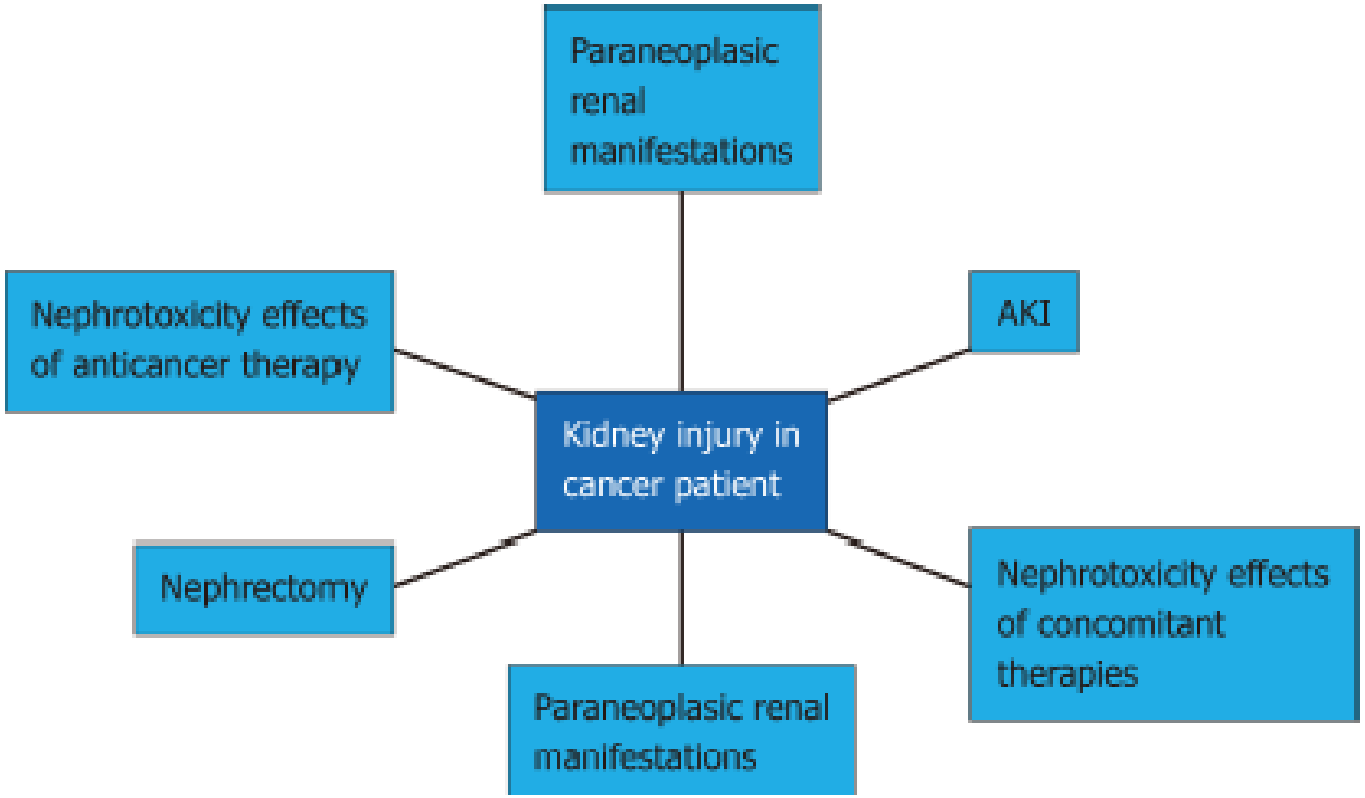


Figure 2 – Kidney damage in cancer patients

AKI:Acute Kidney Injury;

- Many drug-related renal toxicities do not have a clear mechanism of injury or pathophysiology, making it difficult to develop strategies to prevent or minimize their occurrence.
- some factors may contribute to the higher incidence of this side effect, including

  intravascular volume depletion,

  use of non-chemotherapeutic nephrotoxic drugs (analgesics, antibiotics, proton pump inhibitors, and bone-targeted therapies)

  radiographic ion contrast agents or radiation therapy,

  urinary tract obstruction and

  intrinsic kidney disease

- These factors should be considered by the oncologist before starting treatment to minimize the risk of renal toxicity.

Conventional cytotoxic agents

- Alkylating agents
- Antimetabolites
- Antimicrotubule agents
- Antitumor antibiotics
- Platinum agents

Immunomodulatory drugs

- important for the treatment of multiple myeloma.
- Thalidomide : stands out first.
- Studies have shown that there is no relationship between AKI and the use of thalidomide, but the progression of the underlying disease itself.
- However, some case reports have shown hyperkalemia, which does not require dose adjustment, but requires careful monitoring of potassium levels .
- Lenalidomide, an analogue of thalidomide, is mainly metabolized by the kidneys, which puts patients with pre-existing renal impairment at risk and therefore requires dose adjustment.
- Among the findings, AKI including severe renal dysfunction and the need for dialysis was reported.
- Pomalidomide, although primarily metabolized by the liver, was associated with AKI and nephrolithiasis. However, there is no standard for dose adjustment, except for hemodialysis patients.

Molecularly Targeted Agents

- Inhibitors of the epidermal growth factor receptor pathway(EGFRi)
- Human epidermal growth factor receptor 2 inhibitors (HER2i)
- B-cell lymphoma-2 inhibitors(BCL2i)
- Anaplastic lymphoma kinase inhibitors(ALK1i)
- BRAF inhibitors
- Mammalian target of rapamycin inhibitors (mTORi)
- BCR-ABL1 and KIT inhibitors
- Vascular endothelial growth factor pathway inhibitors(VEGFi)
- Burton's tyrosine kinase inhibitor
- Anti CD22 immunotoxin
- Polyadenosine diphosphate ribose polymerase inhibitors
- Immune checkpoint inhibitors (ICI)

Inhibitors of the epidermal growth factor receptor pathway(EGFRi)

- Epidermal growth factor receptor (EGFR) activation leads to receptor tyrosine kinase phosphorylation and initiates signaling pathways that modulate cell differentiation, proliferation, and survival.
- This receptor is a critical target for the treatment of some cancers, such as NSCLC, which can be targeted by administering EGFR-tyrosine kinase inhibitors (EGFR-TKIs) or anti-EGFR monoclonal antibodies.
- Rare cases of nephrotic syndrome with minimal change disease and membranous nephropathy have been associated with the use of gefitinib, an EGFR-TKI .
- This drug family may also cause hypomagnesemia, hypophosphatemia, and hypokalemia.
- On the other hand, increased renal magnesium loss has been associated with the administration of anti-EGFR monoclonal antibodies cetuximab and panitumumab.
- This drug is associated with other very rare complications such as acute kidney injury, nephrotic syndrome, and proliferative glomerulonephritis.

Human epidermal growth factor receptor 2 inhibitors (HER-2i)

- **HER-2** : a receptor overexpressed in some breast and gastric/esophageal cancers.
- Trastuzumab is the precursor and the most successful example among antibodies that target HER-2 antagonism .
- This drug as well as Pertuzumab (a human monoclonal antibody) have been implicated in the development of renal failure, such as AKI , proteinuria, increased serum creatinine, and nephritis.
- In addition, hypertension, hypokalemia, hyponatremia and hypomagnesemia have also been reported.
- Administration of lapatinib, a TKI, has been associated with AKI and hypokalemia. In a small number of patients, hyponatremia, hypomagnesemia and hypertension have also been observed.

B-cell lymphoma-2 inhibitors(BCL-2i)

- The cell intrinsic apoptosis pathway has B-cell leukemia/lymphoma-2 (BCL-2) proteins as critical regulators.
- When such a pathway is disrupted, inappropriate persistence of malignant cells can occur .
- The emergence of Venetoclax, a BCL-2 inhibitor, is a promising solution for the treatment of refractory CLL .
- Despite the benefits, such medication is associated with a significant incidence of tumor lysis syndrome(TLS), leading to electrolyte disturbances and AKI.
- To avoid these effects, a gradual increase in the dose of the drug is recommended to the patient.

Anaplastic lymphoma kinase inhibitors (ALK-1i)

- Anaplastic lymphoma kinase 1 (ALK-1) belongs to the insulin receptor tyrosine kinase family, which plays an important role in regulating cell growth .
- Mutations related to the gene encoding this kinase are associated with malignancies such as anaplastic large cell lymphoma, Hodgkin's lymphoma, non-small cell lung cancer, neuroblastoma, and rhabdomyosarcoma.
- Crizotinib : the first ALK inhibitor developed and has been widely used to treat advanced NSCLC with ALK fusion gene positivity.
- A decrease in GFR has been observed in patients who underwent this treatment.
- However, the early onset of this complication and rapid reversibility after drug discontinuation suggest that this phenomenon is not due to direct renal toxicity of crizotinib.
- This drug has also been associated with the development of complex renal cysts, hyponatremia, and hypokalemia in a limited number of patients.
- However, all of these are reversible upon discontinuation of treatment .

BRAF inhibitors

- BRAF is the gene encoding the human protein called B-Raf, and can increase cell proliferation and carcinogenesis .
- Molecularly targeted therapies aimed at inhibiting it have been used in people with malignant melanoma harboring the BRAF V600E mutation.
- Vemurafenib : is associated with a decrease in creatinine clearance (reversible with discontinuation of treatment) as well as rare cases of AKI, which is more common in men .
- At a lower frequency, the use of another BRAF inhibitor called dabrafenib can also lead to AKI.

Mammalian target of rapamycin inhibitors (mTORi)

- A serine/threonine kinase called mammalian target of rapamycin (mTOR) participates in signaling pathways of growth factors and cytokines associated with oncogenic activity, and its inhibition leads to cell cycle arrest.
- Administration of mTOR inhibitors, such as Temsirolimus(in RCC), is associated with proteinuria and, in some cases, kidney dysfunction .

BCR-ABL1 and KIT inhibitors

- The chromosomal translocation t(9;22)(q34;q11) originating from the Philadelphia chromosome results in a BCR-ABL1 gene rearrangement observed in patients with chronic myeloid leukemia (CML) .
- Bosutinib : is used in the treatment of refractory CML and can lead to hypophosphatemia as well as a reversible decrease in GFR.
- it is recommended to monitor kidney function at the beginning and also while the patient is undergoing this treatment.
- In addition, the dose should be reduced if treatment-induced renal failure occurs.
- Dasatinib : is rarely associated with AKI and proteinuria.
- Imatinib: can be used to treat gastrointestinal stromal tumors beyond CML.
- If used for a long time, such an agent can lead to AKI and CKD, and renal damage appears to be dose-dependent, with higher doses being associated with a higher risk of renal failure.
- imatinib administration is associated with the occurrence of hypophosphatemia .

Vascular endothelial growth factor pathway inhibitors(VEGFi)

- Vascular endothelial growth factor (VEGF) is an essential growth factor that plays a key role in angiogenesis during embryogenesis, wound healing, and tumor growth.
- There are two types of VEGF pathway inhibitors:

VEGF ligand inhibitors, which are VEGF receptor antagonists and are represented by ramucirumab, bevacizumab, and aflibercept. and

small molecule TKIs (ponatinib, sunitinib, regorafenib, sorafenib, cabozantinib, pazopanib, axitinib, vandetanib, cabozantinib, lenvatinib), which prevent the activation of the intracellular domain of the VEGF receptor .

- VEGF is produced by podocytes and binds to its receptors found on the glomerular and peritubular endothelium and mesangial cells.
- This process maintains the glomerular basement membrane structure and proper glomerular function . Therefore, all drugs that block the VEGF pathway may induce renal abnormalities.
- Their renal toxicity is mainly renovascular in nature, including hypertension and proteinuria, occasionally causing nephrotic syndrome, decreased GFR, and TMA, which is rare .

- the exact mechanism of proteinuria and the factors associated with the occurrence and severity of proteinuria are unknown.
- It has been suggested that pre-existing kidney disease (including higher urine protein levels and hypertension) and renal cell carcinoma may be predisposing factors for proteinuria.
- Discontinuation of anti-VEGF drugs improves renal dysfunction, but persistent proteinuria is not uncommon.
- Although ACEis and ARBs may reduce intraglomerular pressure and reduce protein excretion, no recommendation can be made for the use of these agents because there are no controlled studies.
- Although there is insufficient information on renal biopsy in patients treated with VEGF-targeted agents, studies have shown the presence of collapsing glomerulopathy, TMA, and isolated reports of immune complex glomerulonephritis and cryoglobulinemia .

- The most common causative agent is Bevacizumab.
- Less common histological findings with Bevacizumab : nephritic syndrome and AKI .
- In the case of TKIs, proteinuria and hypertension can be seen with their use.
- In addition, AKI and diabetes insipidus have been reported in clinical trials of vandetanib, although the cause has not been established.
- Decreased GFR has been reported during treatment with axitinib, sunitinib, and sorafenib, although renal failure is rare.
- lenvatinib : induces renal failure or impairment,
- Regorafenib : several electrolyte abnormalities, including hypophosphatemia, hypocalcemia, hyponatremia, and hypokalemia .
- In case reports, Sorafenib and Sunitinib have been associated with acute and chronic interstitial nephritis .
- Sorafenib is also known to cause hypophosphatemia and hypocalcemia.

Burton's tyrosine kinase inhibitor

- Ibrutinib is an irreversible Burton tyrosine kinase inhibitor.
- This drug is active in B-cell malignancies and is approved for patients with mantle cell lymphoma or CLL.
- It may be related to AKI and the mechanism of this injury is unclear, but tumor lysis syndrome may contribute.

Anti CD22 immunotoxin

- Moxetumomab pasudotox is used to improve the prognosis of patients with relapsed or refractory hairy cell leukemia.
- Such drug can be associated with AKI and proteinuria.

Polyadenosine diphosphate ribose polymerase inhibitors

- Polyadenosine diphosphate ribose polymerase inhibitors are approved for the treatment of BRCA-mutated breast cancer and platinum-sensitive recurrent epithelial ovarian cancer.
- Creatinine elevations have been reported in some patients treated with olaparib, but in most cases, they are mild.

Immune checkpoint inhibitors (ICPIs)

- The monoclonal antibodies known as checkpoint inhibitors (CPIs) target specific inhibitory receptors present in T cells, as well as in tumor cells and in other immune cells.
- The primary targets for checkpoint inhibition include :

  programmed cell death 1 receptor (PD-1)

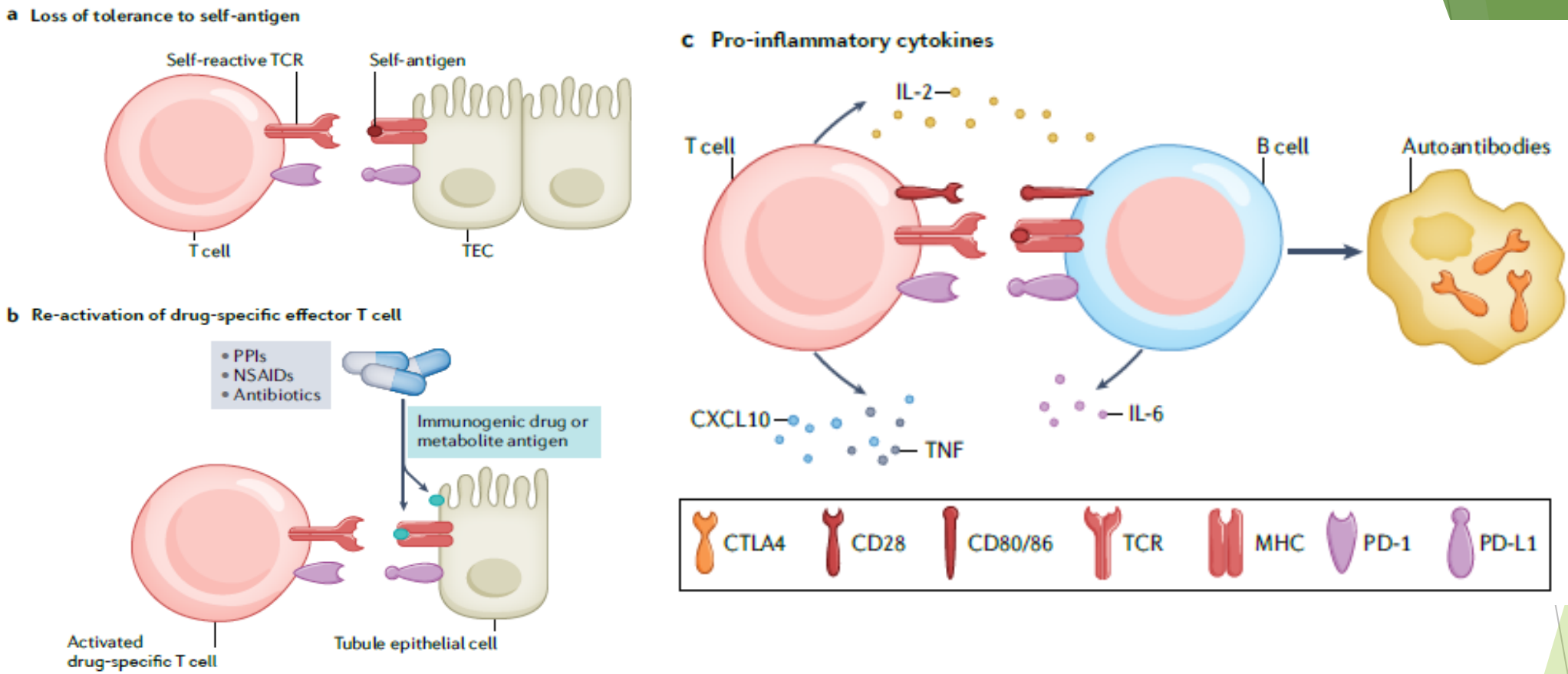
  programmed cell death 1 ligand (PD-L1)

  cytotoxic T lymphocyte-associated antigen 4 (CTLA-4),

that play an important role in negatively regulating T cell activation/function, thus tumor cells carrying PDL-1 or CTLA-4 are protected from immune reactions.

- The objective of checkpoint inhibitors is to restore or generate the activation of the immune system, directed to tumor cells.
- Drugs targeting PD-1 (Nivolumab and Pembrolizumab) and PD-L1 (Atezolizumab, Avelumab, and Durvalumab) have recently demonstrated their potential efficacy in different tumor types (*e.g.*, urothelial carcinoma, NSCLC, melanoma, head and neck cancer, Merkel cell carcinoma, RCC, Hodgkin lymphoma, and microsatellite instability-high or mismatch repair deficient [dMMR] solid tumors) and drugs targeting CTLA-4 (Ipilimumab) is approved for use in patients with advanced melanoma.

- The immune response generated by CPIs may induce immune-related adverse events related to many different organs, including the kidneys.
- AKI is a rare complication of checkpoint inhibitor immunotherapy, being mainly associated with ipilimumab/nivolumab combination therapy (4.9%).
- Various mechanisms have been proposed to underlie the development of ICI-AKI, including loss of tolerance to self-antigens, reactivation of drug-specific effector T cells, and the production of kidney-specific autoantibodies.
- The most commonly reported underlying pathology is acute tubulointerstitial nephritis, but immune complex glomerulonephritis and TMA have also been observed.
- There is also an association between CPIs treatment and electrolyte abnormalities, with hypocalcemia being the most significant.
- Discontinuation of checkpoint inhibitor immunotherapy and treatment with corticosteroids are indicated for patients with severe renal injury.



Pathophysiology of immune checkpoint inhibitor-associated acute kidney injury.

a | the loss of tolerance towards self-antigens. Under normal conditions, self-reactive T cells are silenced by PD-1 signalling, which acts as a checkpoint to diminish T cell responses. In the presence of ICIs, this brake is removed, leading to T cell activation cell damage.

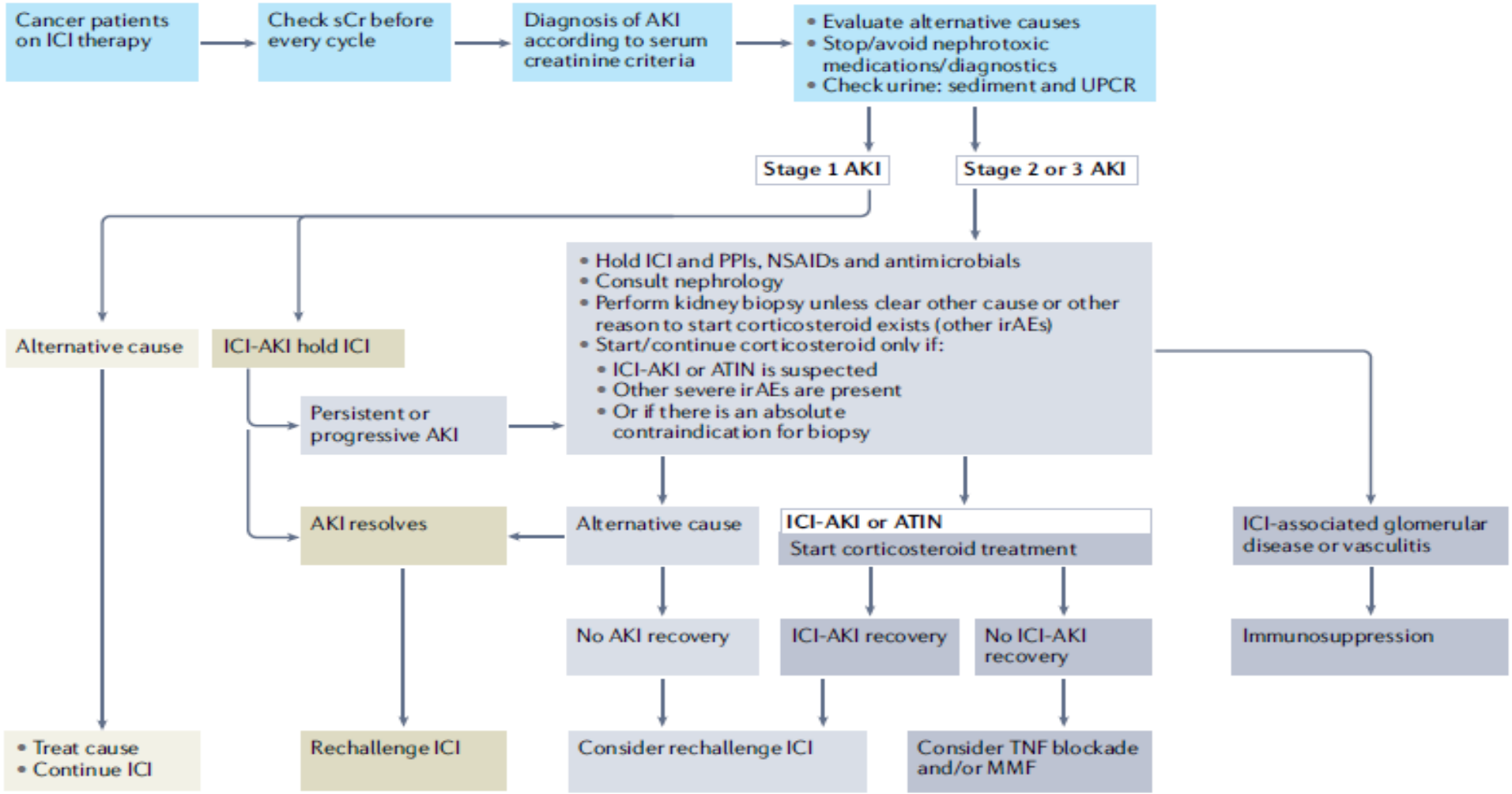
b | re-activation of drug-specific effector T cells. Drugs that are associated with the development of acute tubulointerstitial nephritis (such as proton-pump inhibitors (PPIs), NSAIDs and antibiotics) can trigger an immune response by acting as haptens after binding to tubular antigens either directly or indirectly. These haptens can become trapped in the renal parenchyma, leading to an immune response and tubular damage. These auto-reactive T cells can be present inactived and become activated when ICIs are administered.

c | production of auto-antibodies directed against self-antigens presented by tubule epithelial cells, mesangial cells or podocytes, as a result of increased serum cytokine levels, generating an inflammatory setting. TCR, T cell receptor; TEC, tubule epithelial cell.

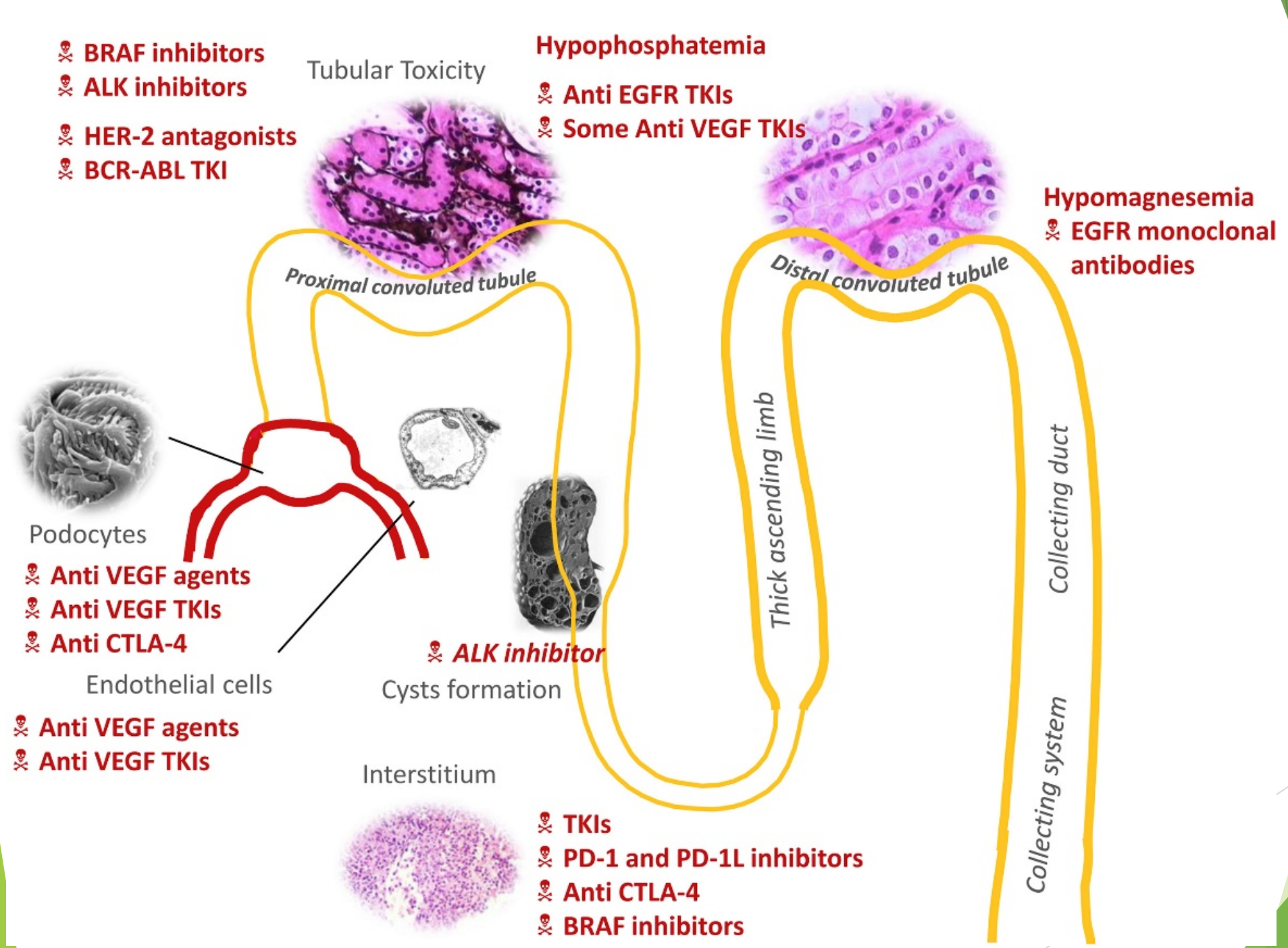
Grade	CTCAE	KDIGO
1	SCr > 1–1.5 × baseline	SCr 1.5–1.9 × baseline
2	SCr > 1.5–3 × baseline	SCr 2–2.9 × baseline
3	SCr > 3 × baseline	SCr ≥ 3 × baseline or initiation of RRT
4	SCr > 6 × baseline	NA

AKI, acute kidney injury; CTCAE, Common Terminology Criteria of Adverse Events; KDIGO, Kidney Disease: Improving Global Outcomes; NA, not applicable; RRT, renal replacement therapy; sCr, serum creatinine.

CTCAE and KDIGO criteria (based on serum creatinine) for acute kidney injury



Proposed approach to the diagnosis and management of immune checkpoint inhibitor-associated acute kidney injury. serum creatinine (sCr) should be monitored before and during ICI treatment. after occurrence of AKI, patients should be evaluated for alternative causes of AKI; nephrotoxic medications should be avoided or stopped, and urinalysis should be performed. In patients with stage 1 ICI-AKI, ICI therapy should be hold until AKI resolves. When AKI is persistent or progressive, a nephrology consult should be obtained, and **a renal biopsy performed unless a clear alternative cause of AKI exists or there is another reason to start corticosteroids**. When ICI-ATIN is histologically proven, steroids should be started and ICI rechallenge can be considered after recovery. When a diagnosis of ICI-associated glomerular disease or vasculitis is made histologically, immunosuppressive treatment can be considered, although there are insufficient data to determine the optimal immunosuppressive agent in this context. irAEs, immune-related adverse events; MMF, mycophenolate mofetil; TNF, tumour necrosis factor.


BRAF inhibitors
ALK inhibitors
HER-2 antagonists
BCR-ABL TKI
Tubular Toxicity
Hypophosphatemia
Anti EGFR TKIs
Some Anti VEGF TKIs
Hypomagnesemia
EGFR monoclonal antibodies
Proximal convoluted tubule
Distal convoluted tubule
Thick ascending limb
Collecting duct
Collecting system
Podocytes
Anti VEGF agents
Anti VEGF TKIs
Anti CTLA-4
ALK inhibitor
Cysts formation
Endothelial cells
Anti VEGF agents
Anti VEGF TKIs
Interstitium
TKIs
PD-1 and PD-1L inhibitors
Anti CTLA-4
BRAF inhibitors

Other biological factors

- Interferon alpha activates the release of interleukin-2, which leads to the death of cancer cells.
- Recombinant alpha interferon can cause proteinuria, which can range from nephrotic to AKI, the pathology consistent with minimal change disease or focal segmental glomerulosclerosis .
- Rarely, TMA is seen, and in this situation, immediate discontinuation of the drug is critical .
- IL-2 is used to treat metastatic renal cell carcinoma and metastatic melanoma.
- IL-2 treatment induces a cytokine-driven capillary leak syndrome that leads to intravascular volume depletion, AKI (prerenal azotemia) , edema , and a reversible decrease in GFR.
- It is important to emphasize that acute ischemic tubular injury may also occur due to severe hypotension.
- Cytokine-mediated inflammatory kidney injury may also occur .

- Lutetium peptide receptor radioligand Lu 177-dotatate is a radiolabeled somatostatin analog with potential antineoplastic activities.
- Lutetium Lu 177-dotatate binds to somatostatin receptors expressed by various neuroendocrine tumor cells.
- When the radioligand binds to that receptor, the complex enters, resulting in beta rays reaching cells that express somatostatin receptors.
- Kidney radiation may lead to glomerular damage with renal failure.
- Amino acid solution injection is needed to protect the kidneys from the effects of radionuclide therapy. This protocol results in a low rate of renal toxicity during treatment. No risk factors for renal toxicity have been identified.

Conclusion

- Key points in patients affected by nephrotoxicity due to anti-cancer drugs :

  close monitoring,

  proper hydration and

  dose reduction, with suspension of the agent use if necessary.

- It is also important to conduct more controlled studies in the sense of creating guidelines for dose adjustment in patients with renal impairment, since most of the dose adjustment standards for these drugs are being created recently through studies with small numbers of subjects and in initial stages of clinical trials.


Thanks for your attention