Nephrologist Role in Oncology- Hematology Consults

Shokoufeh Savaj MD

Professor of Iran University of Medical Sciences

Firoozgar Hospital

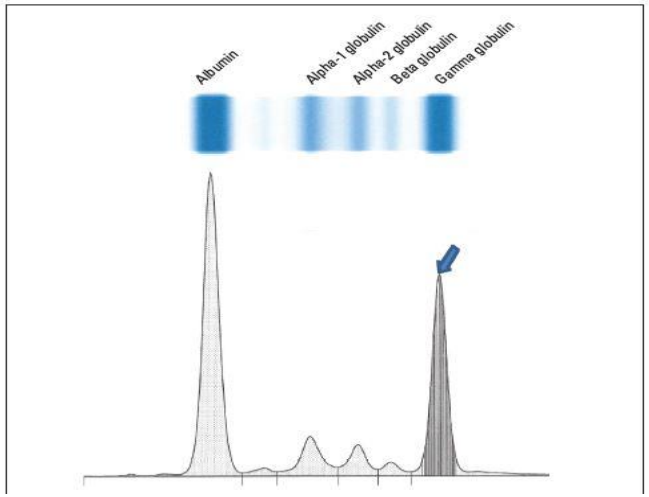
Introduction

- During the past decades survival of patients with cancer have been improved.
- An increasing number of cancer survivors have or will develop kidney disease associated with malignancy or its treatment.
- A variety of renal complications can occur among cancer patients, including acute kidney injury (AKI), chronic kidney disease (CKD), proteinuria and nephrotic syndrome, and electrolyte disorders.

Case :1, Cancer and AKI

- A 63 years old man consulted due to increased serum creatinine in the last three months . He complains of low back pain and fatigue.
- BUN : 31 mg/dl, Serum Creatinine : 2.3 mg ,Hgb : 10.1 gr/dl , ESR : 88 mm , Calcium : 10.6 mg/dl, Urine analysis : protein 1+ , RBC : 3-4hpf , WBC : 2-3 hpf , 24 hours protein : 1550 mg
- Secondary GN lab tests negative
- SPEP : M component
- Free serum light chain kappa/lambda : 0.1

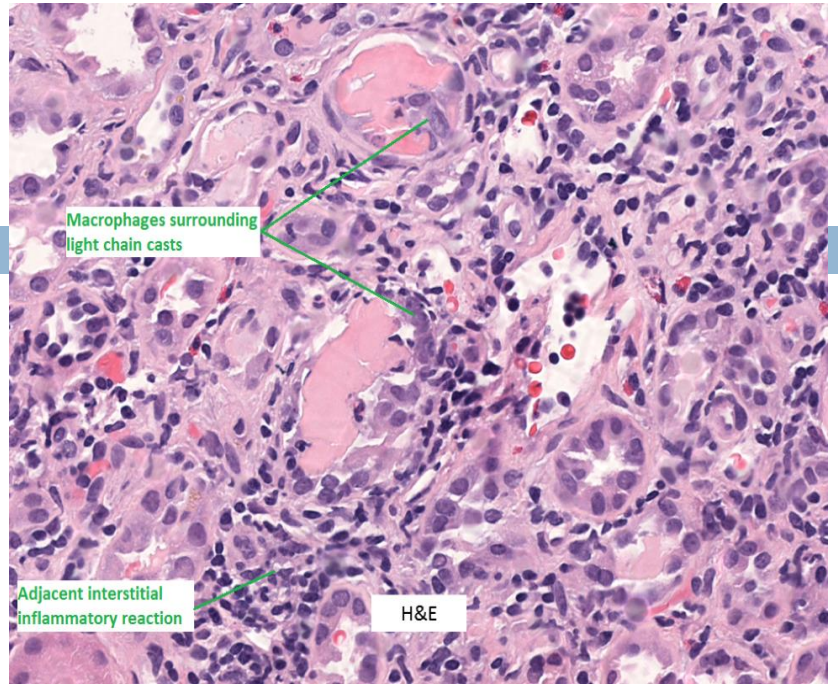
  (0.26- 1.65)

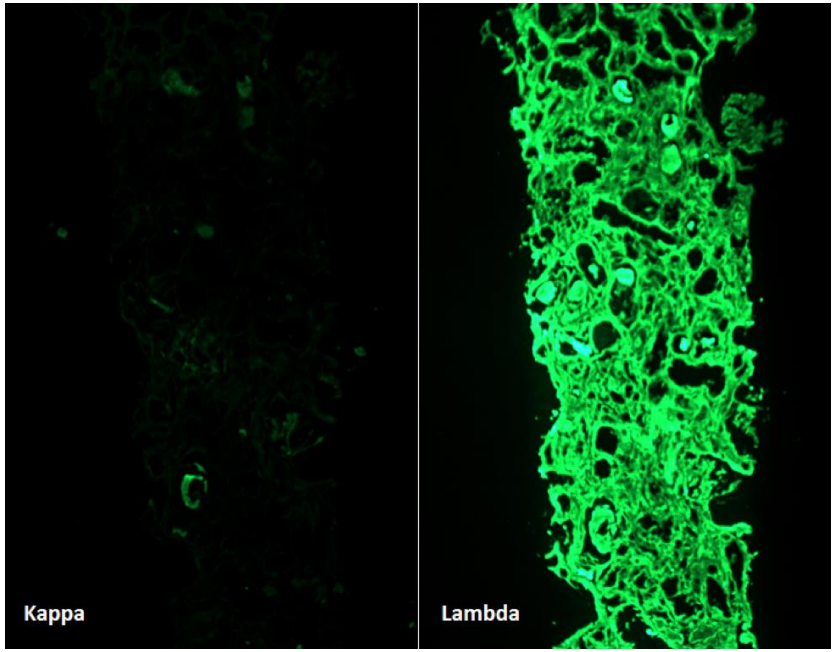


Recognizing a monoclonal protein (M-protein) in the serum and urine

Total serum protein	Non Specific
Serum protein electrophoresis (SPEP)	Abnormal protein in Gama, α2 region, β region
Serum immunofixation	differentiate a monoclonal from a polyclonal increase in immunoglobulins and to determine the type of immunoglobulin involved (eg, IgG kappa). This test does not quantify the M-protein. Detects serum M protein at a concentration of at least 0.02 g/dL.
Serum free light chain (FLC) assay	More sensitive for detecting light chain , results may be affected by the presence of renal failure.
Dipstick testing	Unable to show light chain
Urine protein electrophoresis (UPEP)	For measurement, total monoclonal protein 24 hours should be collected
Urine immunofixation	Urine immunofixation is more sensitive than UPEP, but cannot estimate the size of the monoclonal protein. Detects urine M protein at a concentration of ≥0.004 g/dL.

- kidney involvement is the most complication of MM and its prevalence is around 50%. In 30% of patients kidney injury diagnosed at the presentation of disease
- Light chain cast nephropathy can occur when large amounts of monoclonal free light chains are produced by plasma cell clones.
- Risk factors : volume depletion, metabolic acidosis, hypercalciuria, loop diuretics, NSAID, Contrast media





Acute kidney injury In Multiple Myeloma

- Light Chain nephropathy
- Hypercalcemia
- Hyperuricemia
- Interstitial nephritis
- Plasma cell infiltration
- Thrombotic Microangiopathy (TMA)
- Hyperviscosity
- Crystal Storing Histiocytosis

Nephrotoxic drugs

- Contrast agents
- NSAID
- Lenalidomide
- Bisphosphonate (Zalendronic acid)
- Proteasome inhibitors: TMA

Carfilzomid : Tumor lysis Syndrome (TLS)

Treatment

- Hydration (Urine output> 3liter per day if not contraindicated)
- Stop nephrotoxic agents
- Treatment of hypercalcemia and hyperuricemia
- Anti myeloma therapy (Dexametasone, Bortesomib, Cyclophosphamide
- High cutoff hemodialysis or plasmapheresis (evidence not enough)

High cutoff versus high-flux haemodialysis for myeloma cast nephropathy in patients receiving bortezomib-based chemotherapy (EuLITE): a phase 2 randomised controlled trial

Colin A Hutchison*, Paul Cockwell*, Veronica Moroz, Arthur R Bradwell, Lesley Fifer, Julian D Gillmore, Mark D Jesky, Markus Storr, Julie Wessels, Christopher G Winearls, Katja Weisel, Nils Heyne, Mark Cook

- In this open-label, phase 2, multicentre, randomised controlled trial (EuLITE), ‚newly diagnosed multiple myeloma, biopsy-confirmed cast nephropathy, and acute kidney injury that required dialysis from renal services in 16 hospitals in the UK and Germany.
- Primary outcome was independence from dialysis at 90 days.
- In this phase 2 study, HCO-HD did not improve clinical outcomes for patients with de novo multiple myeloma and myeloma cast nephropathy who required haemodialysis for acute kidney injury and who received a bortezomib-based chemotherapy regimen relative to those receiving HF-HD. These results do not support proceeding to a phase 3 study for HCO-HD in these patients.

Lancet 2019

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

Risk Factors For Chemotherapy-induced Nephrotoxicity

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 combinations enhance nephrotoxicity like :NSAIDS, aminoglycosides, and radiocontrast

Patient Factors

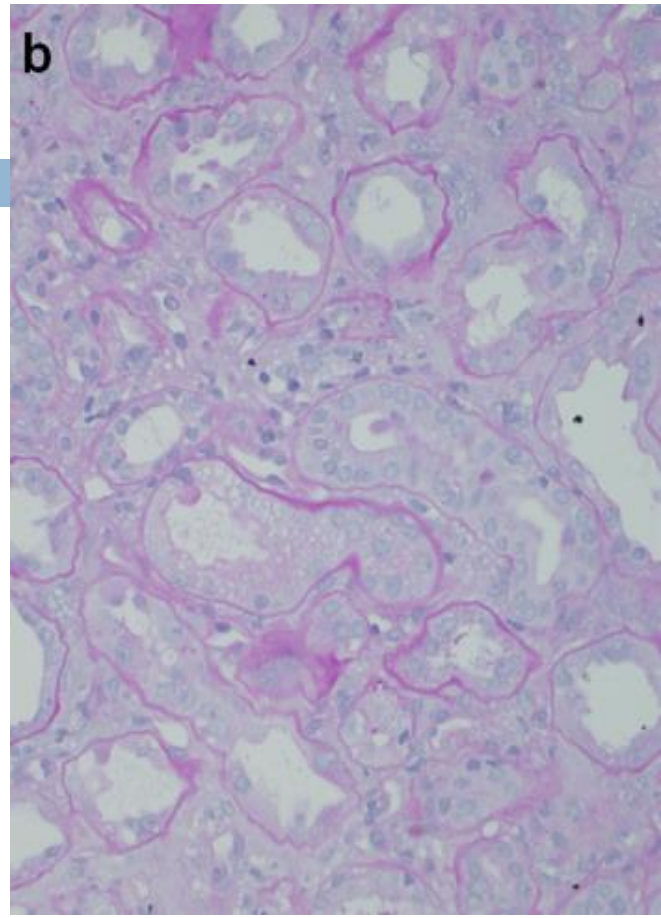
- Older Age
- Underlying AKI Or CKD
- Immune Response Genes
- Increased Allergic Reactions To Drugs
- Pharmacogenetics Favoring Drug/Toxin Toxicity Gene Mutations In Hepatic And Renal CYP450
- Enzyme Systems
- Gene Mutations In Transport Proteins And Renal Transporters

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

Case 2 : Conventional chemotherapy

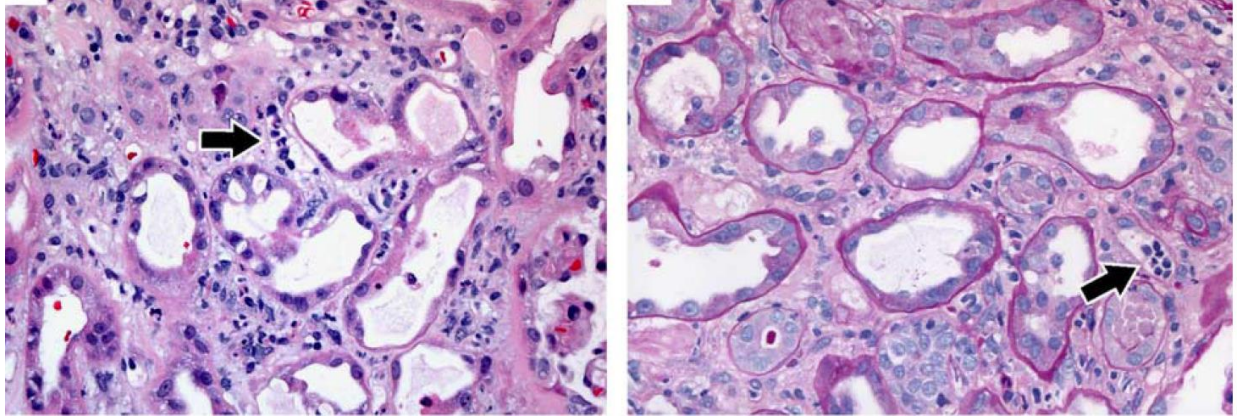
- A 64-year-old man with a thoracic esophageal cancer referred for neoadjuvant chemotherapy . He had squamous cell carcinoma and chemotherapy protocol was 80 mg/m^2 cisplatin on day 1 and 800 mg/m^2 5-fluorouracil on days 1–5. On day 3, however, his serum creatinine increased to 3.35 mg/ml that needed hemodialysis on day 6 with a serum creatinine around 8.35 mg /dl .On the day 36 and renal biopsy done. In 49 months follow up there was not any recurrence of tumor but no improvement in kidney function.



Diffuse mild interstitial infiltration of lymphocytes, vacuolar degeneration in the proximal tubules, mild interstitial fibrosis, and moderate arteriolar sclerosis

Sasaki et al, Int J Surg Case Rep. 2016

Cisplatin



Solid tumors such as ovarian, testicular,bladder, colorectal, lung, and head and neck cancers.

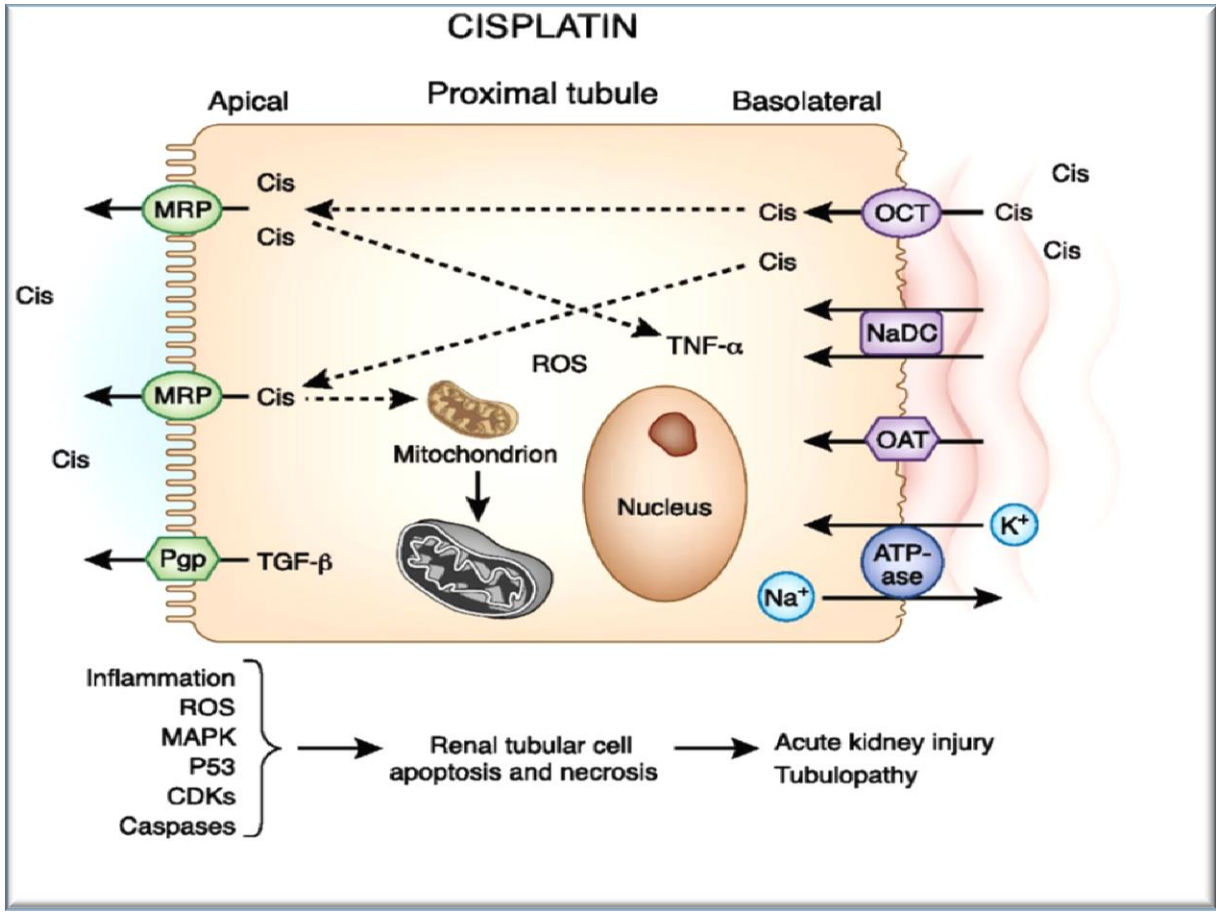
Kidney injury is seen in about 1/3 of cisplatin-treated Patients on day 3-7 after treatment .

OCT2 is highly expressed at the basolateral tubular cell Membrane Cisplatin is concentrated 5-fold in proximal tubular cells relative to serum.

Cisplatin cross links DNA and activates other injury pathways such as caspase, mitogen-activated protein kinase, and p53, then incites apoptosis and inflammation.

It causes Distal RTA, Fanconi like syndrome ,Salt losing nephropathy, Hypomagnesemia, TMA, AKI

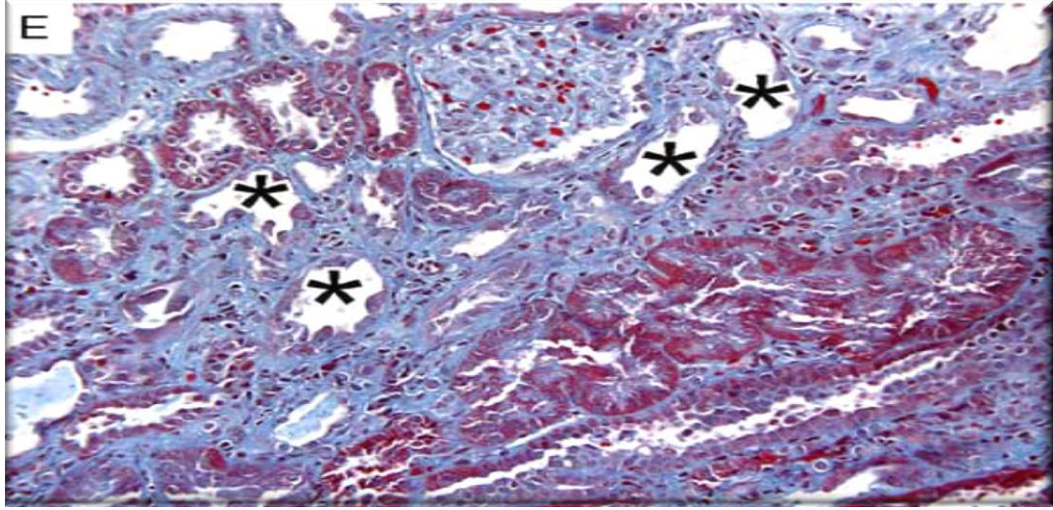
Next generations have lower affinity for OCT2.



Prevention Cisplatin Nephrotoxicity

- 1000 mL of isotonic saline plus 20 mEq of potassium chloride and 2 grams of magnesium sulfate. two to three hours prior to, and a minimum of 500 mL over the two hours following, the cisplatin administration to establish a urine flow of at least 100 mL/hour for two hours prior to, and two hours after, chemotherapy administration
- Mannitol may be appropriate in select patients, such as those treated with high-dose cisplatin ($\geq$100 mg/m^2) and/or those with pre-existing hypertension .The addition of furosemide is generally not required, unless there is evidence of fluid overload.
- Avoidance of nephrotoxic drugs
- Dose reduction
- Cisplatin analogs : Carboplatin
- Amifostine, Sodium thiosulfate ,N-acetylcysteine , theophylline ,glycine ,peroxisome proliferator-activated receptor (PPAR)-alpha ligand ,polymeric cisplatin nanoparticles, cell cycle inhibitors ,and lithium .However, none of these agents have an established role in patients being treated with cisplatin.

Alkalating agents: Ifosfamide



Treatment of metastatic germ-cell testicular cancer and some sarcomas causes 30% nephrotoxicity.

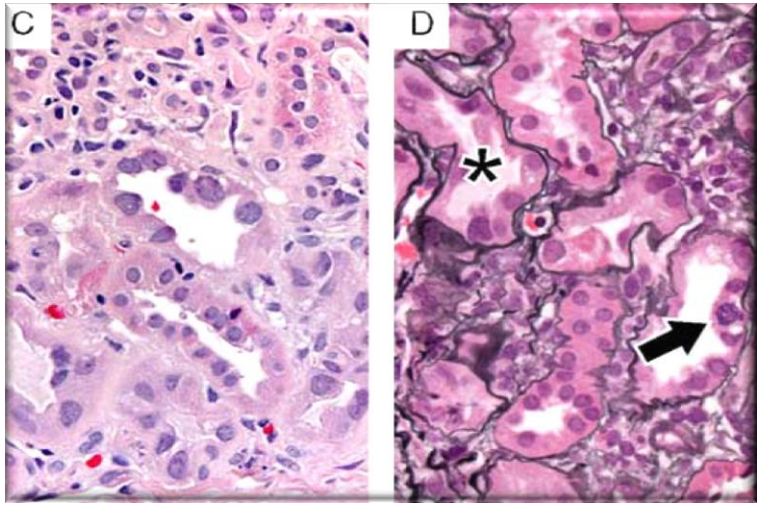
Ifosfamide is metabolized into active (nitrogen mustard) compounds that alkylate DNA, damaging it and leading to cell death.

Like cisplatin ,Ifosfamide enters renal tubular epithelial cells by the OCT2 transporter.

Glucosuria, aminoaciduria, tubular proteinuria and rarely, polyuria due to nephrogenic diabetes insipidus, hypophosphatemia, hypokalemia ,normal anion gap hyperchloremic metabolic acidosis, and, AKI..

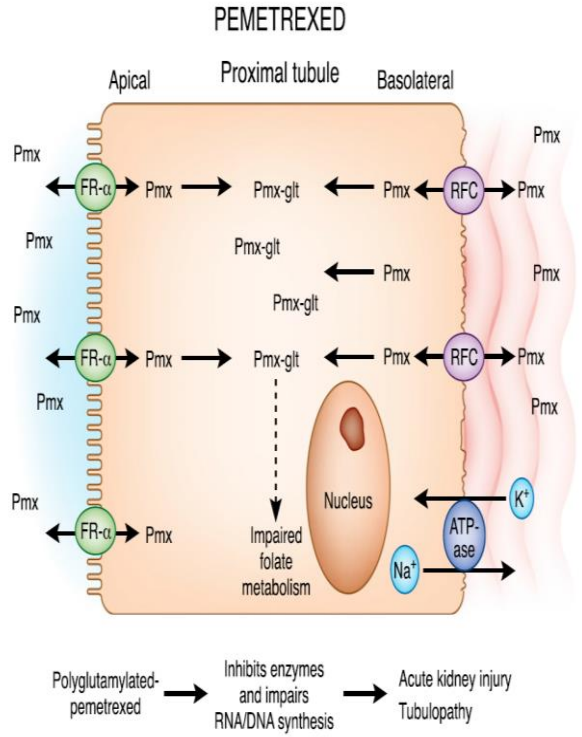
Dose modification(<total dose above 60 g/m^2), Mesna,N acetycysteine

Antimetabolites: Pemetrexed



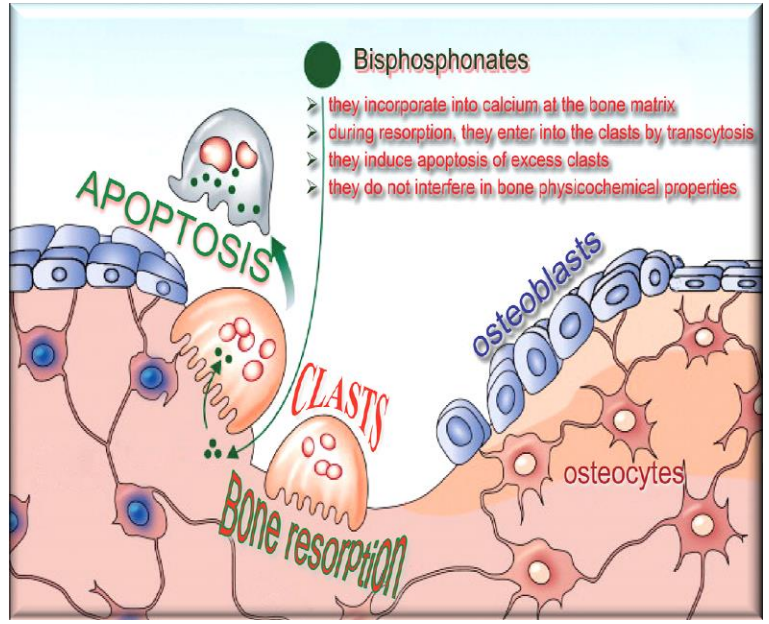
Pemetrexed is an antifolate agent that inhibits Enzymes involved in purine/pyrimidine metabolism, thereby impairing RNA/DNA synthesis

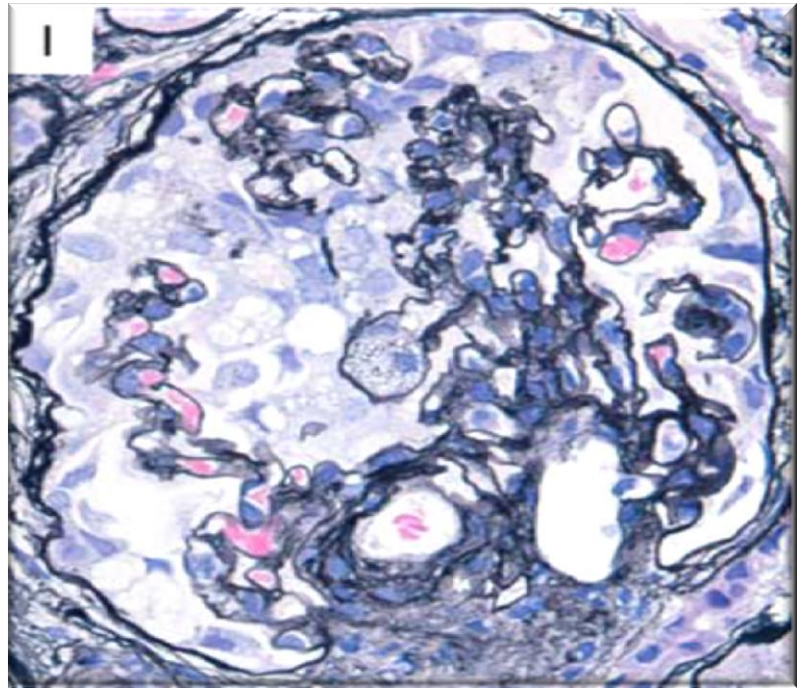
Indication :mesothelioma and non-small cell lung cancer ATN ,AIN, DI, mild proteinuria and RTA are described in Pemetrexed nephrotoxicity.



Bisphosphonate

- Indication :treatment of metastatic bone cancer and to treat hyper calcemia of malignancy, act by inhibiting osteoclastic bone resorption.
- Collapsing focal and segmental glomerulo nephritis with nonreversible renal failure has been reported with pamidronate.
- Zoledronate has been associated with acute tubular necrosis.
- FSGS (of no special type) and Minimal change disease reported





Perazella MA, et al. Kidney Int. 2008;74:1385–1393.

Proteasome inhibitors:

Bortezomib, Carfilozomib, Ixazomib, ,Aresenic Trioxide,etoposide

- AKI,TMA, ATN, Prerenal Azotemia

Antimetabolites :

Cladribine ,Fludarabine, Clefaraine ,Gemicitabine, , Hydroxyureas ,Methotrexate ,Pemetrexed

- AKI, Kidney Dysfunction, TMA, Falsely Increased Creatinine ,ATN, SIADH, Functional Kidney Impairment, RTA, DI

Antitumor antibiotics

Antracyclines :

Daunorubicin, Doxorubicin

Mitomycin C

- MCD, FSGS, TMA in Pegulated form of Doxorubicin

Antimicrotubule Agents:

Cabazitaxel

Vinca alkaloids : Vincristine, Vinblastin , Vinorelbine

- **AKI, Hemorrhagic Cystitis, SIADH**

Immune Modulatory Drugs

Thalidomide, lenalidomide

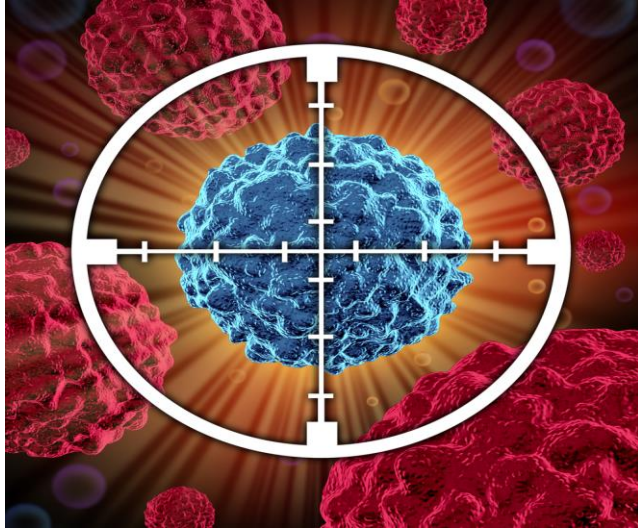
- **AIN, AKI, Hyperkalemia**

Alkalating agent :

Cyclophosphamide,Ifosphamide, , Melphalan,Nitrosureas:Carmustine, Lamustine ,Sterptozocin

- **SIADH, Hemorrhagic Cystitis , FLS, Polyuria , Chronic Interstitial Nephritis, Uric Acid Nephrolithiasis, ATN, AIN**

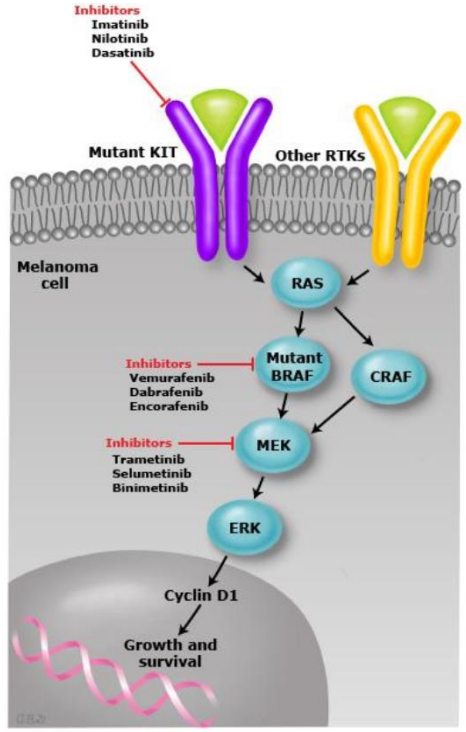
Targeted Therapy



Most targeted therapies are either small-molecule drugs or monoclonal antibodies.

Small-molecule drugs are small enough to enter cells easily, so they are used for targets that are inside cells.

Monoclonal antibodies are drugs that are not able to enter cells easily. Instead, they attach to specific targets on the outer surface of cancer cells.



Serine/Threonine-protein Kinase B-raf

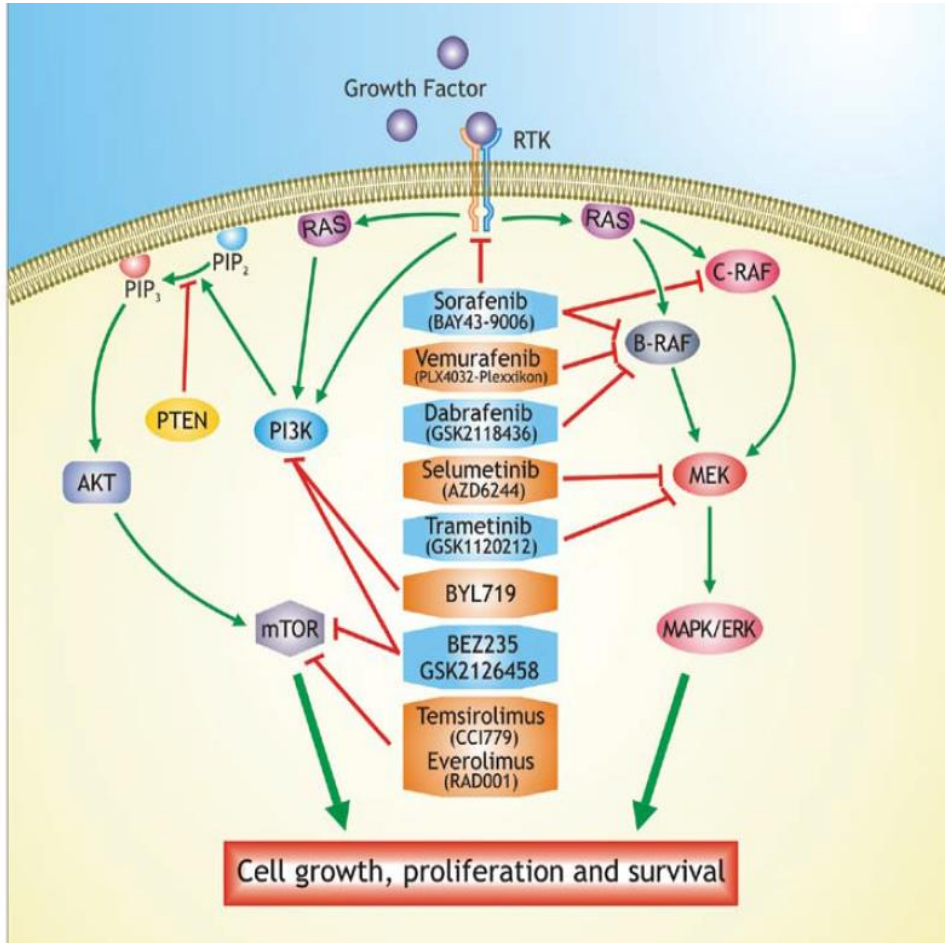
The B-Raf protein is involved in sending signals inside cells which are involved in directing cell growth.

Many melanomas, colon cancers, thyroid cancers, Langerhans cell histiocytosis, and hairy cell leukemias harbor activating point mutations in the serine-threonine kinase BRAF

Two of B-Raf inhibitors are Vemurafenib And Dabrafenib.

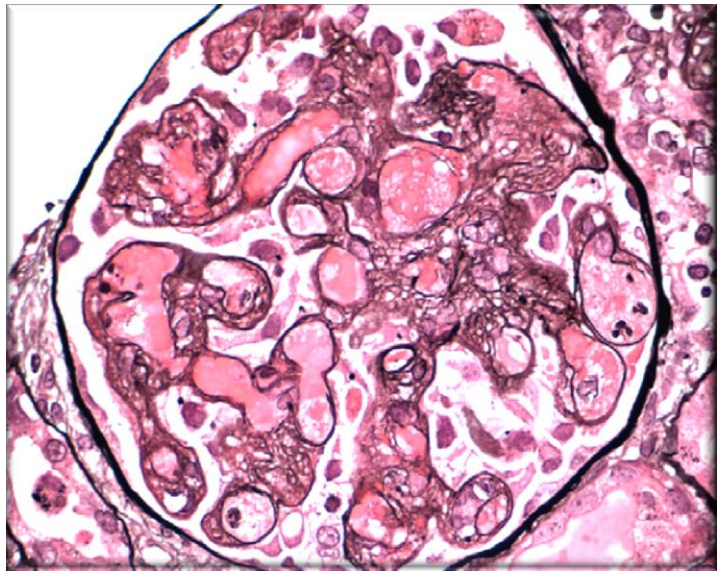
In a Review of adverse events reported to the FDA included 14 cases of electrolyte disorders and132 cases of AKI with vemurafinib and 13 with dabrafenib as of June 2014.

Electrolyte disorders have also been reported, including Fanconi syndrome, hypophosphatemia, hyponatremia, and Hypokalemia.

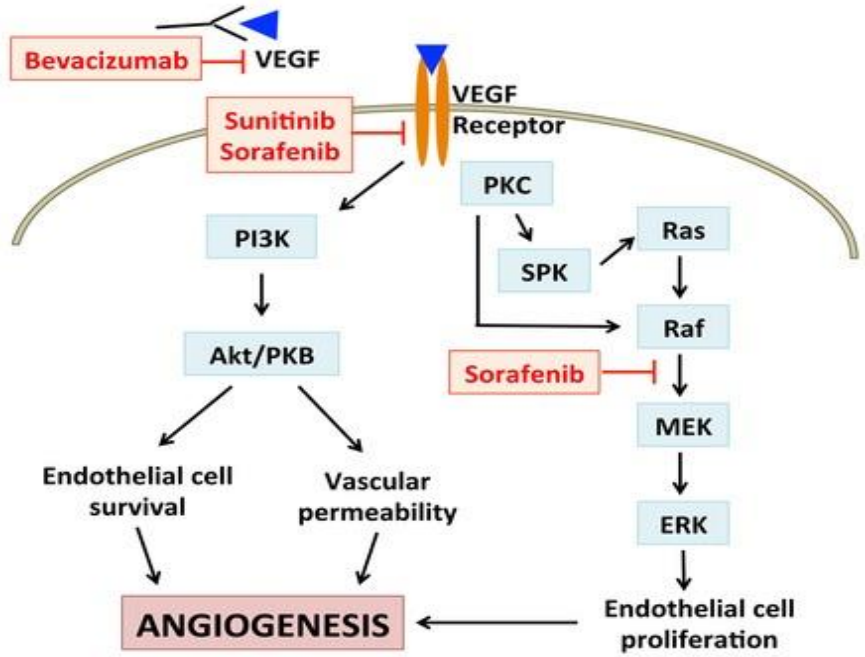


Jhaveri KD, et al. Nephrotoxicity of the BRAF inhibitors vemurafenib and dabrafenib. JAMA Oncol.2015;

VEGF Inhibitors



- They are associated with increased blood pressure (20-25%).
- 31 published cases of VEGF inhibitor–related kidney injury at biopsy and reported 3 with interstitial nephritis, 11 cases of glomerulonephritis, and 15 cases of thrombotic microangiopathy
- Glomerulonephritis included immune complex–mediated (IgA and cryoglobulin), crescentic, minimal change, and FSGS, collapsing type.



Usui J et al , Human Pathology 2014

Chimeric Monoclonal Antibody Against EGF Receptor (EGFR)

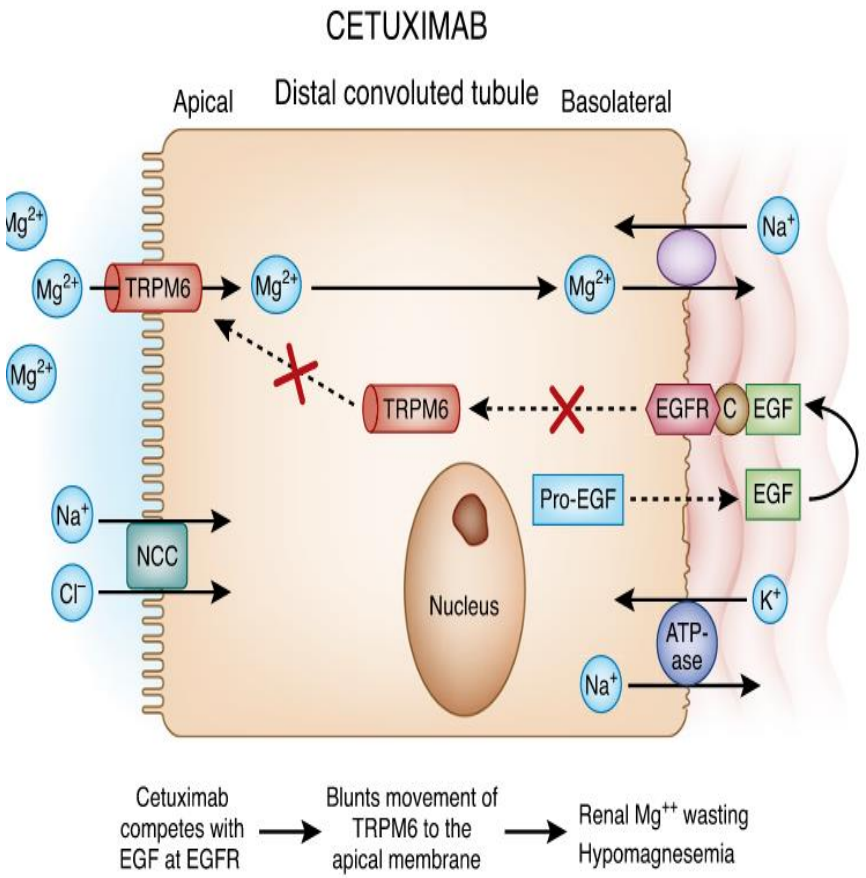
Cetuximab

Indication :Colorectal, head/neck, breast, and lung cancers

EGF overexpression present in these malignancies reduces apoptosis and enhances tumor cell growth

Cetuximab has a 10-fold greater affinity for EGFR than natural ligand Hypomagnesemia happens in half of the patients.

Panitumumab is also complicated by hypomagnesemia (36%).



Renal Vasculature

Hemodynamic AKI (capillary leak syndrome)

- IL-2, Denileukin Diftitox

Thrombotic microangiopathy

- Antiangiogenesis drugs (Bevacizumab and Tyrosine Kinase Inhibitors)
- Gemcitabine And Cisplatin
- Mitomycin C and IFN

Glomeruli

Minimal Change Disease

- Interferon
- Pamidronate

Focal Segmental Glomerulosclerosis

- Interferon
- Pamidronate
- Zoledronate (Rare)

Acute Interstitial Nephritis

- Sorafenib And Sunitinib

Crystal Nephropathy

- Methotrexate

Tubular Damage

Acute Tubular Necrosis

- Platinums, Zoledronate, Ifosfamide, Mithramycin
- Pentostatin, Imatinib, Diaziquone, Pemetrexed

Tubulopathies

Fanconi Syndrome

- Cisplatin, Ifosfamide, Azacitadine,
- Diaziquone, Imatinib, Pemetrexed

Salt Wasting

- Cisplatin . Azacitadine

Magnesium Wasting

- Cisplatin, Cetuximab, Panitumumab

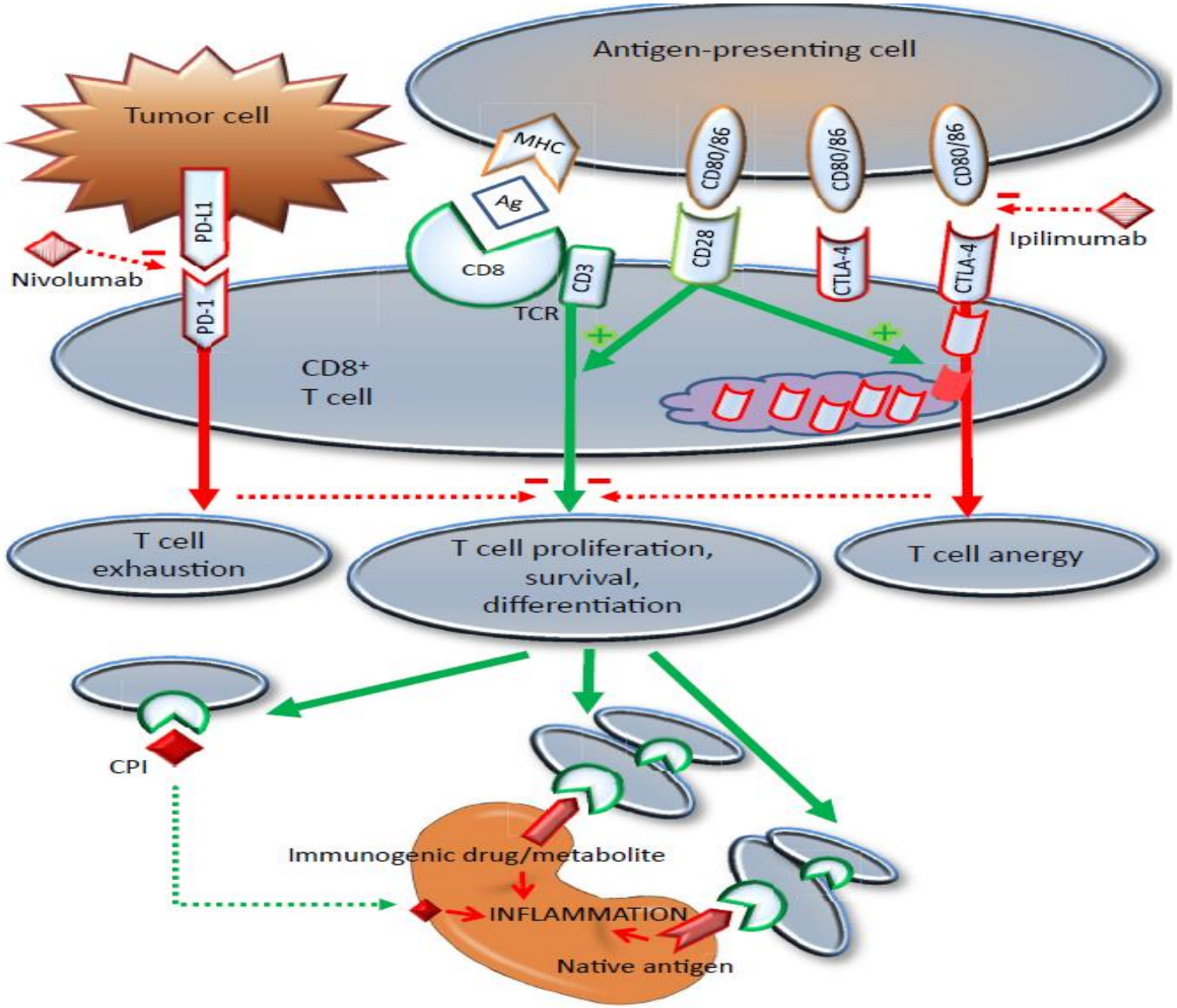
Nephrogenic Diabetes Insipidus

- Cisplatin, Ifosfamide, And Pemetrexed

SIADH

- Cyclophosphamide , Vincristine

Check Point Inhibitors



Shingarev et al AJKD 2019

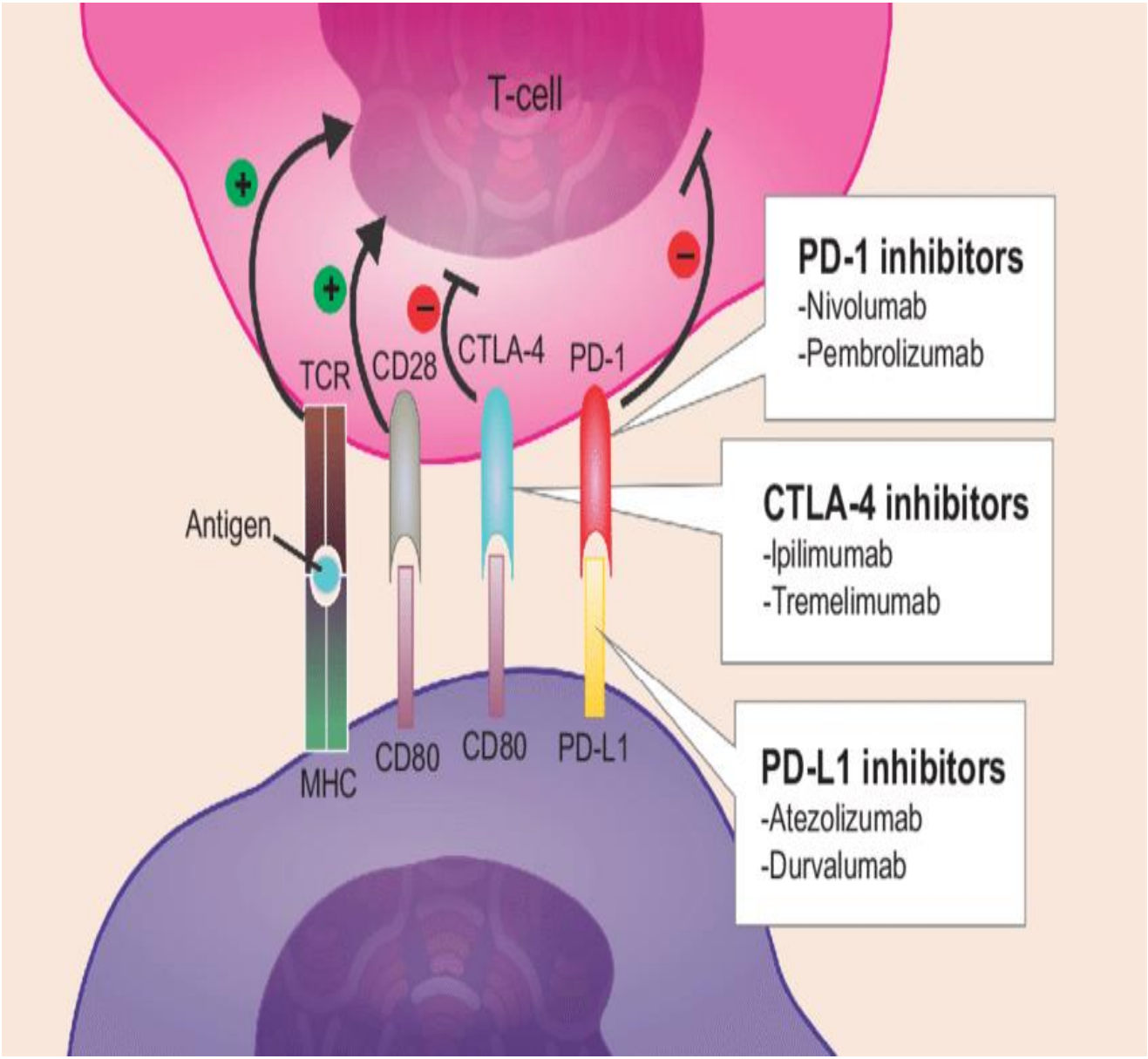
Mechanism of Action Of Immune Checkpoint Inhibitors

T regs depend on the activity of CTLA-4, PD-1, and PD-L1 to induce immunosuppression.

Ipilimumab and tremelimumab are monoclonal antibodies that inhibit CTLA-4.

Nivolumab, Pembrolizumab, Atezolizumab, and Durvalumab inhibit PD-1 and PD-L1.

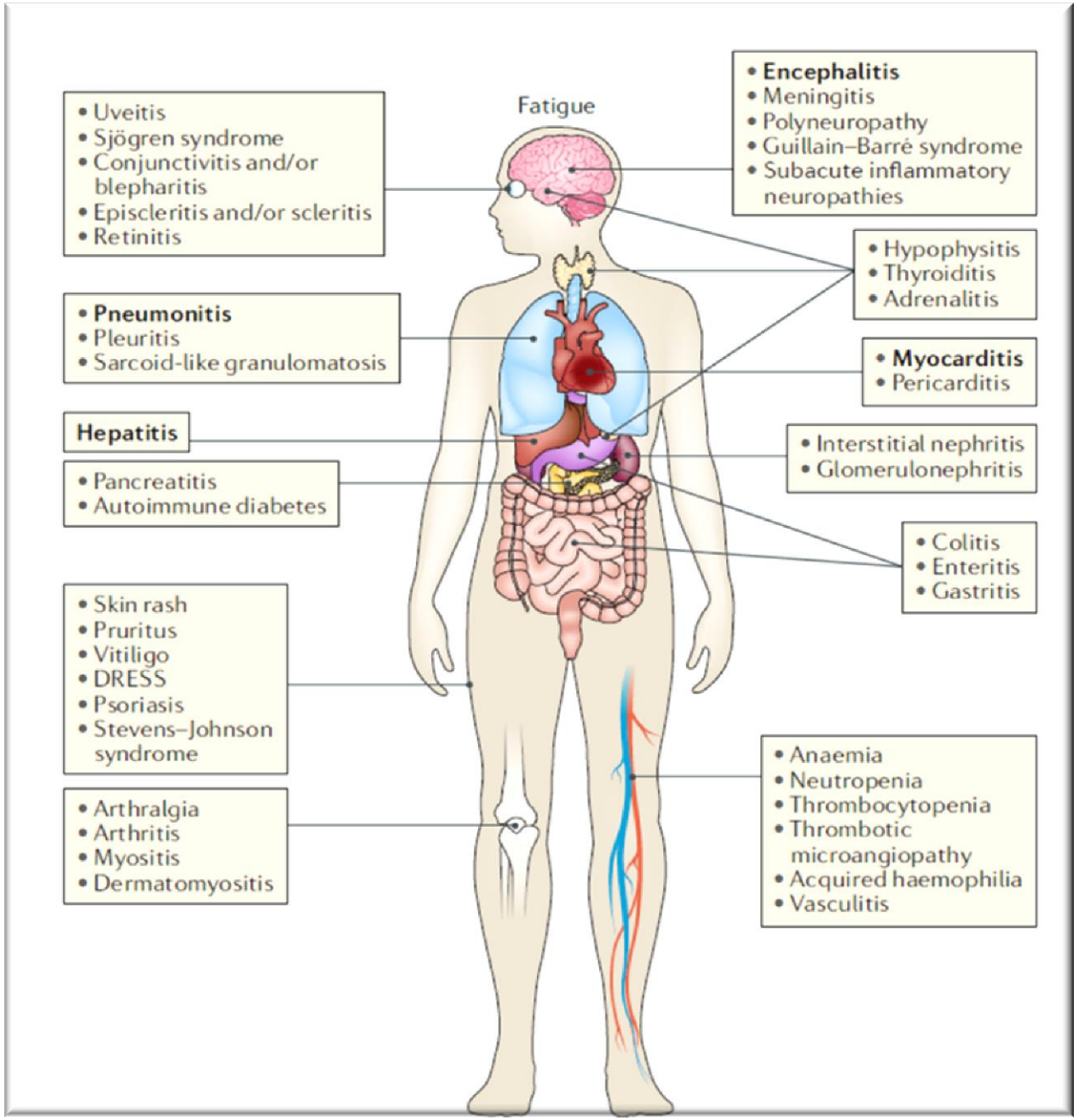
These drugs act by reducing immuno checkpoint activity on a T reg –rich microenvironment, thus diminishing tumor evasion.



De Mello et al OncoTargets and Therapy 10:21-30 · December 2016

Case 3 : Check point inhibitors

- A 57-year-old man was admitted to our department with AKI. He had been diagnosed with stage IIA adenocarcinoma of the lung (T2aN1M0) four years previously. After the surgical resection of the left lower lobe of the lung, the patient received four courses of carboplatin and paclitaxel. However, two years after the initial diagnosis, the cancer progressed to stage IV (T0N3M1b) with multiple metastases to the lung, bone, and brain. Radiotherapy followed by repeated courses of multiple chemotherapies with cisplatin, pemetrexed, and bevacizumab was not effective. The patient was then started on biweekly treatments with **Nivolumab** (170 mg, by intravenous drip infusion). After four courses of treatment, an acute increase was observed in the patient's serum creatinine level (from 0.80 mg/dL to 1.57 mg/dL). He was referred and admitted.
- U/A : pyuria, Protein 1+ , Serum Creatinine : 2.8 mg/dl, Secondary GN: Negative, Renal Biopsy was done



immune- related adverse events in check point inhibitors

- **Thrombotic microangiopathy**

(can be restricted to kidney)

- **Acute interstitial Nephritis**
- **Lupus nephritis**
- **Minimal Change Disease**
- **Immune complex Glomerulitis**

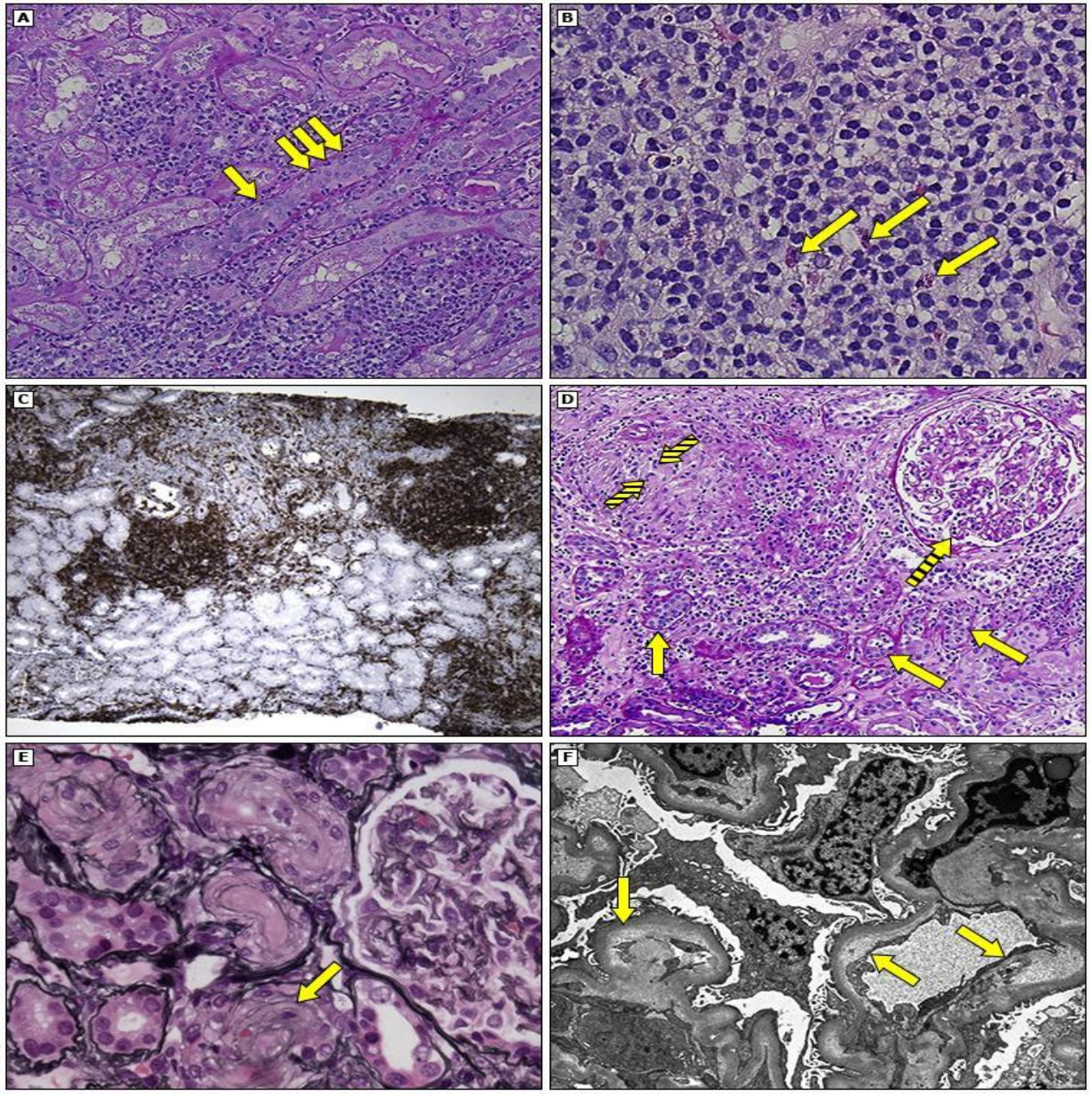
Martins et al, Nature reviews in clinical oncology , 2019

Programmed cell death protein 1 inhibitor treatment is associated with acute kidney injury and hypocalcemia: meta-analysis

Sandhya Manohar[1], Panagiotis Kompotiatis[1], Charat Thongprayoon[2], Wisit Cheungpasitporn[3], Joerg Herrmann[4] and Sandra M. Herrmann[1]

- **Meta-analysis Of Clinical Trials That Monitored Electrolyte Levels And Kidney Functions**
- **During Treatment With Nivolumab Or Pembrolizumab By Searching MEDLINE, EMBASE And The Cochrane Database From Inception Through April 2017.**
- **The pooled estimated incidence rates of AKI and hypocalcemia in patients treated with PD-1 inhibitors were 2.2% (95% CI 1.5–3.0%) and 1.0% (95% CI 0.6–1.8%), respectively.**
- **Among patients who developed AKI with PD-1 inhibitors, the pooled estimated rate of interstitial nephritis was 16.6% (95% CI 10.2–26.0%).**

Nephrol Dial Transplant (2019) 34: 108–117



(A) Periodic acid-Schiff stain shows diffuse interstitial inflammation and focal severe tubulitis with infiltrating lymphocytes.
(B) H&E stain shows diffuse interstitial infiltrates predominantly composed of lymphocytes, with several eosinophils
(C) Immunohistochemistry reveals the lymphocytic infiltrates in the interstitium to be predominantly CD4b T cells .
(D) Periodic acid-Schiff stain shows a noncaseating granuloma with multinucleated giant cells (striped arrows), severe interstitial inflammation and tubulitis (arrows), and severe glomerulitis (dashed arrow).
(E) Silver stain shows diffusely wrinkled glomerular basement membranes and "onion-skin" lesion of small arteries
(F) Electron microscopy shows swollen endothelium and subintimal widening filled with electron-lucent "fluffy" material

Case Report

AJKD

2019

Renal Vasculitis and Pauci-immune Glomerulonephritis Associated With Immune Checkpoint Inhibitors

Alexander J. Gallan, Ellen Alexander, Pankti Reid, Fouad Kutuby, Anthony Chang, and Kammi J. Henriksen

- **4 cases of renal vasculitis or pauci-immune glomerulonephritis after checkpoint inhibitor therapy.**
- **The time from checkpoint inhibitor initiation to immune-related adverse event presentation ranged from 2 weeks to 24 months.**
- **Three patients were treated with glucocorticoids, resulting in clinical resolution.**

- Grade 1 toxicity, an increase increatinine by 0.3 mg/dl or 1.5–2.0 times above baseline, should prompt temporary cessation of immune checkpointinhibitor treatment and review of other potential causes ofAKI.
- Grade 2 toxicity (increase increatinine from two to three times baseline) Discontinuation of immunecheckpoint inhibitor therapy and using prednisone0.5–1 mg/kg per day for and increasing this to 1–2 mg/kg per day
- Grade 3 (increase in creatinine above three times baseline or.4.0 mg/dl) or grade 4 toxicity (requirement for dialysis orlife-threatening complications). Steroids should be slowly tapered over several weeks. Addition of immunosuppression can be considered for high-grade toxicity not responsive to therapy.
- These guidelines do not recommend a kidney biopsy when other causes of AKI can be excluded on clinical grounds. If nonspecific clinical presentation of immune-related adverse events in the kidney exist, a biopsy recommended

Cortazar FB et al .J Am Soc Nephrol31:435–446, 2020

Case 4

- A 70-year-old man with ADPKD received a kidney transplant with alemtuzumab induction followed by steroid avoidance immunosuppression with tacrolimus and mycophenolic acid. Seven years later, the patient noticed a pruritic, nonbleeding, nonhealing sore over his left temple biopsy showed SCC. There was a recurrence after beginning of mTor inhibitors and immunosuppression minimization. One years later bone and lymph node metastasis reported. Treatment with an immune checkpoint inhibitor (nivolumab) was recommended.

Systematic Review of the Safety of Immune Checkpoint Inhibitors Among KidneyTransplant Patients

- Systematic review of 27 articles till April 2019
- a total of 44 Ktx patients treated with immune checkpoint inhibitorwere identified. Of 44 Ktx patients, 18 were reported to have acute rejection. Median time from immunecheckpoint inhibitors to acute rejection diagnosis was 24 (interquartile range, 10–60) days. Reported types of acute allograft rejection were cellular rejection (33%), mixed cellular and antibody-mediated rejection(17%), and unspecified type (50%). Fifteen (83%) had allograft failure and 8 (44%) died.
- Three patients had a partial remission (17%), 1 patient achieved cancer response (6%), and 5 patients had stable disease (28%).

Sandhya Manohar et al , Kidney International Reports (2020)5,149–158

Investigations that should be performed before any anticancer treatment

Step 1:Evaluate kidney function

Step 2: Evaluate nutritional status, comorbidities, ongoing (and previous) therapies

Step 3 : check the drugs

Step4 : Risk factors of Evaluate the risk of AKI/CKD

Cancer, Drug , patient

Step 5 :Plan adequate measures to prevent AKI and other organs' toxicity during the treatment

Jolanta Malyszkoet al ,KI ,2020

مشورت در کارها واجب شود
تا پشیمانی در آخر کم شود
مولانا