Acute Kidney Injury Associated with Cancer: Focus on Chemotherapeutic Nephrotoxicity

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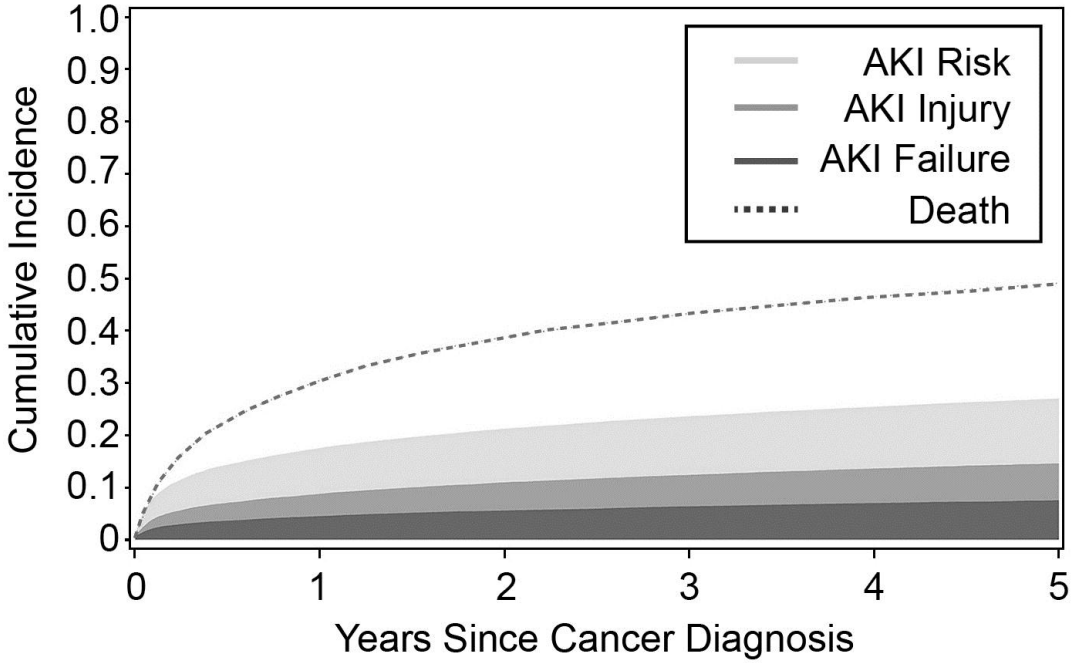
AKI in Patients with Malignancies

- Common occurrence
- Negative impacts across the care continuum
  - Impacts chemotherapeutic regimens
  - Longer length of stay
  - Lower cancer remission rates
  - Higher mortality
- Differences in etiologies, prevention and therapies between solid and hematological malignancies

AKI Epidemiology: Population

- Denmark: among 1.2 M people, there were 37,267 incident cancer patients between 1999-2006.
- One-year risk of AKI: 17.5% (>50% rise in SCr)
- Five-year risk of AKI: 27%
- Highest risk among kidney cancer (44%), liver cancer (33%) and myeloma (31.8%)



AKI is common among cancer patients

Christiansen, Johansen et al., Eur J Intern Med 2011

AKI in Hospitalized Cancer Pts

- Among all admissions in a cancer ICU (288)

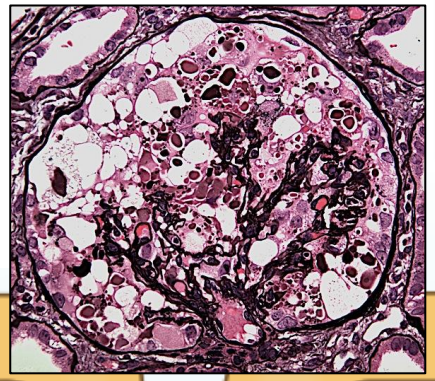
Change in SCr	(%)	Mortality (%)
None	45.9	13.6
>50% rise	33.3	49
>100% rise	10.4	62.3
>200% or HD	10.4	86.8

Liborio, Abreu et al., Oncology, 2011

Chemotherapy drug-induced injury: Multiple sites along the Nephron

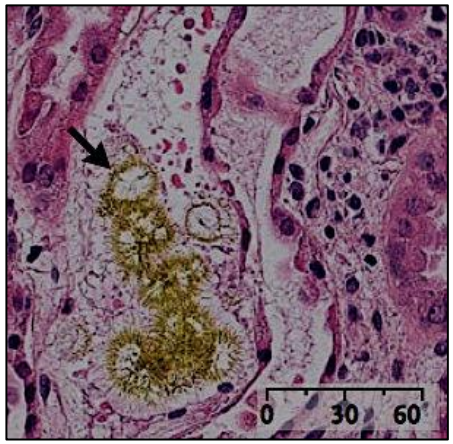
Pamidronate, Interferon,
Anti-angiogenesis Drugs

FSGS



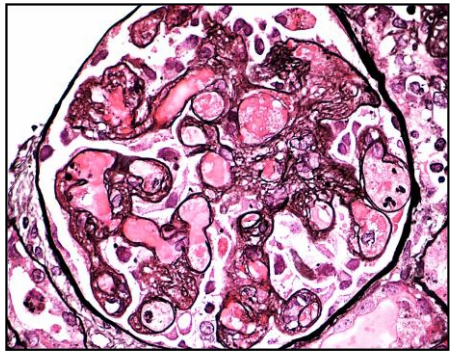
Methotrexate

Crystalline nephropathy



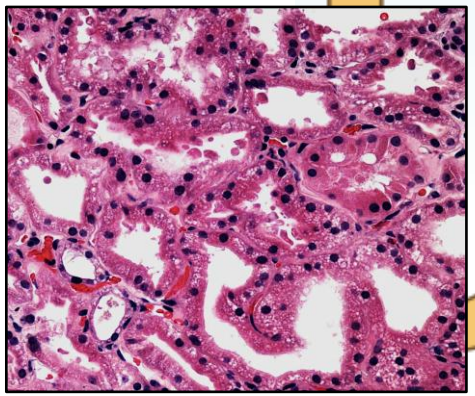
Mitomycin C, Gemcitabine
Anti-angiogenesis Drugs

TMA



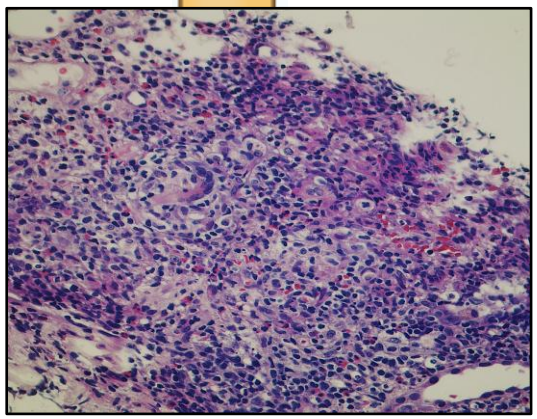
Platinums
Ifosfamide
Pemetrexed
Crizotinib
Zoledronate

ATI



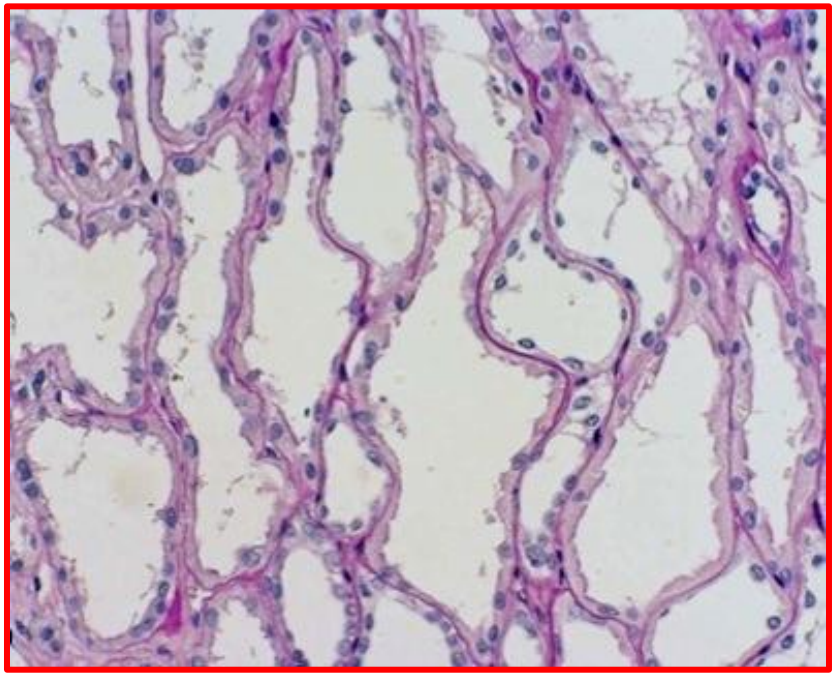
Checkpoint Inhibitors
TKIs, BRAF inhibitors

TIN

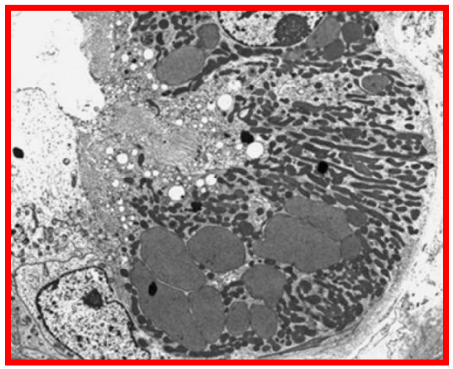


Acute tubular injury/ATN

- **Cisplatin**
- **Ifosfamide**
- **Zoledronate**
- **Pentostatin**
- **Imatinib**
- **Pemetrexed**
- **Others**



Courtesy of Gilbert Moeckel



Cisplatin

- Cisplatin is a platinum compound that is an effective therapy for many cancers
- Major adverse effect is nephrotoxicity (ototoxicity)
- Both are dose-related toxicities
  - Apoptosis and necrosis
- Nephrotoxic manifestations include:
  - Tubulopathies: Fanconi syndrome, salt wasting, magnesium wasting, and nephrogenic DI
  - AKI: increased vascular resistance and tubular injury with ATN; TMA (HUS) seen rarely
- Nephrotoxicity is often reversible, but can be permanent with CKD and chronic tubulopathies

Cisplatin

- Prevention of AKI/Tubulopathies
  - Forced diuresis with IV NS/ Hypertonic (3%) saline
  - Amifostine
    - Glutathione analog taken up by normal cells
    - Complicated by N/V
  - Sodium thiosulfate
  - Other agents:
    - nucleophilic sulfur thiols, neurotrophins, phosphonic acid, melanocortins, free oxygen radical scavengers
  - Other Platinums (carboplatin, oxalaplatin)
    - Less nephrotoxic than cisplatin
      - Not transported by OCT-2
      - Cl^- at ***cis*** position in cisplatin replaced by carboxylate and cyclobutane in carboplatin/oxalaplatin

Ifosfamide

- Ifosfamide is an alkylating agent utilized for certain cancers
- Major adverse effect is nephrotoxicity (vs hemorrhagic cystitis with cyclophosphamide)
- Cytoxan's major toxic metabolite is acrolein; ifosfamide's major toxic metabolite is chloracetaldehyde
- Nephrotoxic manifestations include:
  - Tubulopathies: Proximal tubular injury/Fanconi syndrome, and nephrogenic diabetes insipidus
  - AKI: acute tubular injury/necrosis with single or multiple high doses
- AKI is often reversible, but can be permanent

Ifosfamide

- Prevention:
  - Mesna given with ifosfamide of limited value
  - Dose reduction
  - Cimetidine to block OCT2 transport into the cell (?)
- Treatment:
  - Supportive care, supplement electrolyte deficiencies, monitor for CKD and permanent kidney injury
- Long term:
  - Permanent tubulopathy (1%)
  - Isolated renal phosphaturia (20%)
    - May cause osteomalacia or growth problems in children
    - May cause/exacerbate osteoporosis in elderly

Crystal Nephropathy: Methotrexate

- Acute and chronic nephrotoxicity resulting from precipitation and deposition of crystals (most often uric acid or methotrexate) within the renal tubular lumen.
- Risk increased when tubular urine flow rates are low (volume depletion)
- Risk also increased with GFR < 60 ml/min or with excessive drug dosing

Adv Chronic Kid Dis 21;56-63 (2014)

Methotrexate

- 90% cleared by kidney
- Precipitation in tubules enhanced by acidic pH
  - Urinary alkalinization results in 5- to 8-fold increase in MTX solubility
- AKI manifests as non-oliguric and is often associated with high serum drug and metabolite levels.
- Risk of MTX levels subsequently rising and leading to severe bone marrow suppression and neurotoxicity

Methotrexate

High Risk Patient
-High dose
-Volume depletion
-Acid urine

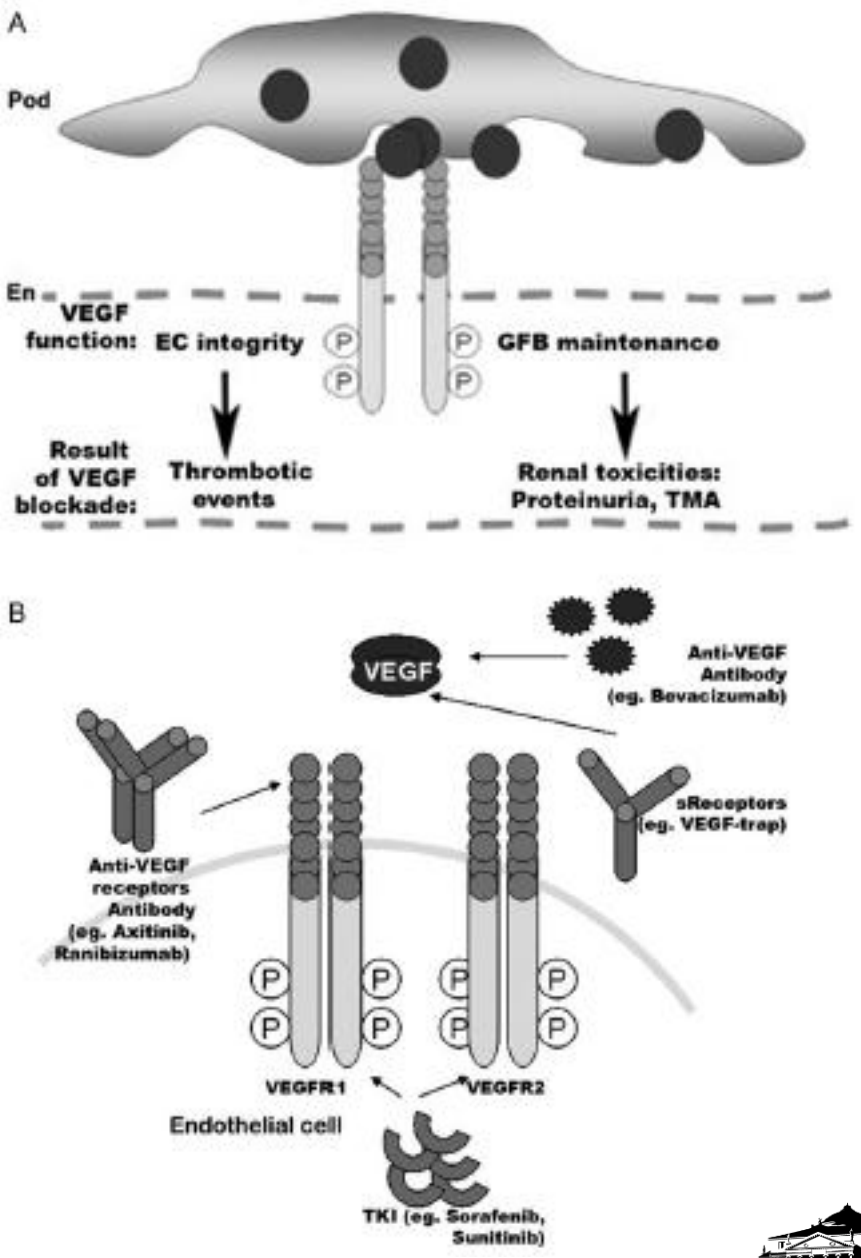
Preventative Measures
-IV fluids
-Urine alkalinization
-Leukovorin rescue

If AKI:
Leukovorin rescue
Glucarpidase
High flux HD (rebound)

Glucarpidase
-Metabolizes MTX to soluble, nontoxic derivatives
-Rapid action
-Measurement of MTX levels once given is problematic
-No rebound

Adv Chronic Kid Dis 21;56-63 (2014)

VEGF Therapies and Renal Toxicities



Lamiere N. Clin Kidney J 2013;0:1-12

VEGF Targeted Cancer Therapies

- VEGF growth of vasculature in tissues; inhibition reduces vasculature growth- treatment of cancers.
- VEGF is also integral in normal functioning of fenestrated endothelial cells; induces and maintains fenestration.
- VEGFR1 and VEGFR2 mediate the permeability of endothelial cells.
- Renal adverse events occur secondary to off-(tumor) target VEGF and VEGFRs.

Renal-Related Adverse Effects to Anti-VEGF Treatments

- Hypertension: decreased endothelial NO production and vasoconstriction; secondary to kidney injury.
  - Occurs within 3-4 weeks of initiation
  - Dose-related
  - Biomarker of anti-tumor efficacy (PFS and OS)
  - Controlled with anti-hypertensives
  - Watch BP upon stopping treatment – acute declines in BP

- Proteinuria: knock-down of VEGF in podocytes
  - Discontinue for Grade 4
  - ACEI/ARBs

- AIN
- Thrombotic Microangiopathy
- Elevations in serum creatinine

VEGF Targeted Therapies

- VEGF targeted therapeutic antibodies
- Bevacizumab (VEGF-A)
  - Proteinuria 21-64%
  - Elevations in SCr – rare
  - Thrombotic microangiopathy

Tyrosine Kinase Inhibitors: Target the VEGFRs (VEGFR1 and VEGFR2)

	Hypertension	Proteinuria	SCr Elevations	TMA	AIN
Sorafenib	17%	1-10%	NR	NR	NR
Sunitinib	27% to 34%	<1%	>10% (RCC: 70%; GIST: 12%)	rare	<1%
Panzopanib	40%	<10%	NR	rare	<1%
Axitinib	40%	5%	55%	1-15%	NR
Cabozantinib	33% to 61%	2% to 12%	58%	NR	NR
Regorafenib	30% to 59%	33% to 84%	NR	NR	NR
Ponatinib	53% to 74%	NR	21%	<1% Post-marketing	NR
Vandetanib	>10% to <33%	10%	16%	NR	NR
Lenvatinib	45% to 73%	26% to 34%	2% to 3%	NR	NR

EGFR Targeted Cancer Therapies

- EGFR involved in cancer growth
- Family of 4 TKs
  - erbB-1 (EGFR)
  - erbB-2 (Her2)
  - erbB-3
  - erbB-4

- Six binding ligands
  - EGF, TGF, ampiregulin, betacellulin, epiregulin, heparin-binding EGF

- TKIs: erlotinib, gefitinib, lapatinib
- Monoclonal abs: cetuximab, panitinumab, trastuzumab, pertuzumab, ertuxmaxomab

- EGFR expressed in proximal and distal tubules, collecting duct, glomerular capillary walls, mesangial cells, parietal epithelial cells, peritubular capillaries and arterioles.

- Renal adverse events occur secondary to off-(tumor) target EGF and EGFRs.

Renal-Related Adverse Effects to Anti-EGFR Treatments

- Nephrotic syndrome
- Proteinuria
- Interstitial infiltration of lymphocytes
- Interstitial damage from the inhibition of normal turnover of tubular epithelial cells
- Magnesium wasting – may also be a biomarker for treatment response
  - most relevant for cetuximab and panitumumab – up to 34% incidence

EGFR Targeted TKI Cancer Therapies

	Proteinuria	SCr Elevations	AIN
Erlotinib	NR	<1%	NR
Gefitinib	8% to 35%	2%	NR
Lapatinib	NR	NR	NR
Neratinib	NR	NR	NR
Vandetanib	10%	16%	NR
Dacomitinib	NR	24%	NR

PDGF Targeted Cancer Therapies

- PDGF-α and PDGF-β
- PDGF-β expression in proximal tubules, mesangium, interstitial cells

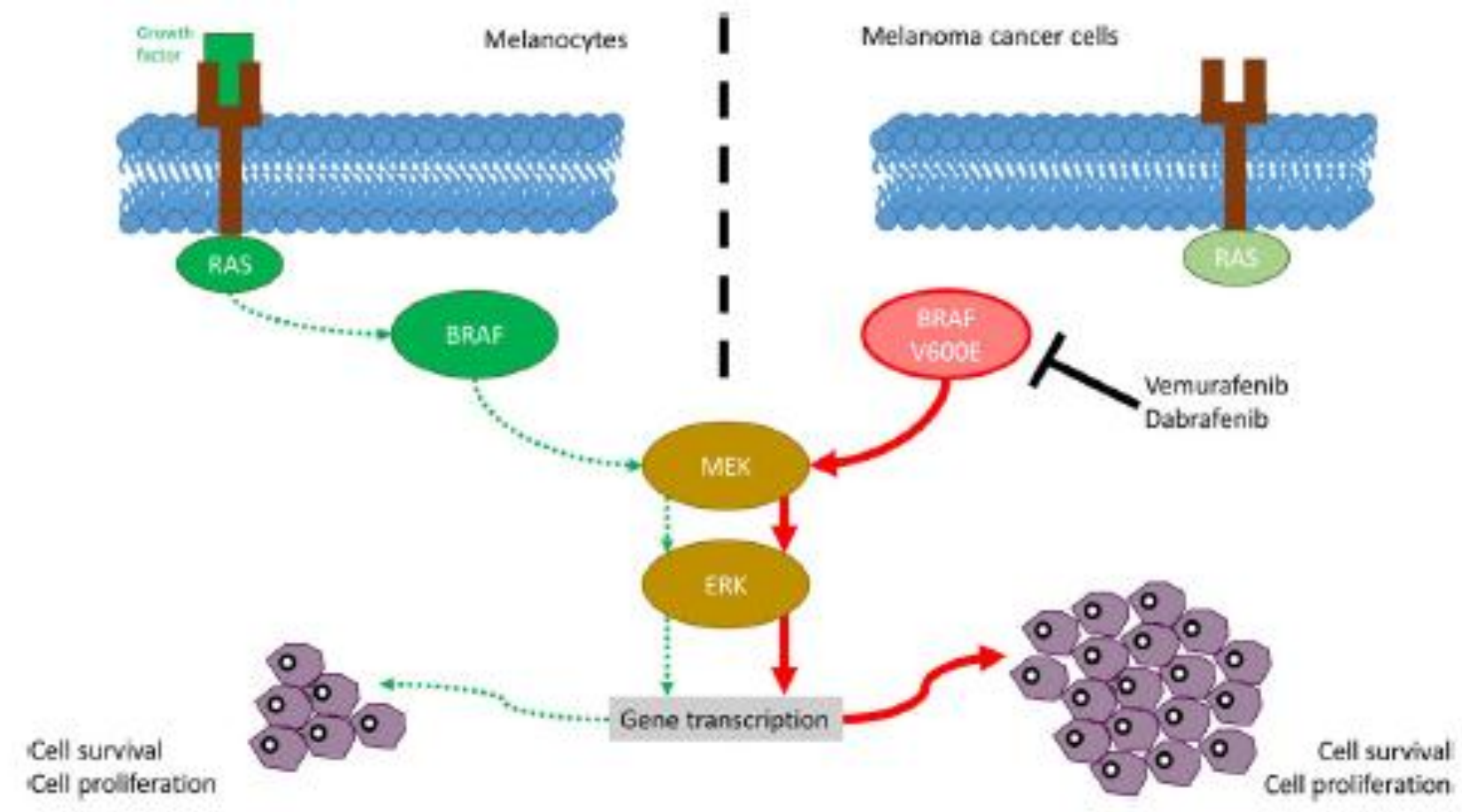
- Renal related adverse effects to PDGFR targeted treatments:
  - acute tubular necrosis
  - thrombotic microangiopathy
  - Fanconi syndrome
  - Tubular vacuolization of both proximal and distal tubules

PDGF Targeted Cancer Therapies

	ATN	Fanconi Syndrome	SCr Elevations	TMA
Imatinib	NR	NR	≤44%	NR
Nilotinib	NR	NR	<1% Post-marketing case reports	NR

Other PDGF acting agents were mentioned in previous classes: Sunitinib, Sorafenib, Pazopanib, Nilotinib, Ponatinib, Axitinib

BRAF Inhibitors



Wanchoo R, et al., Clin Kidney J 2016;9:245-51.

Renal Related Toxicities to BRAF Inhibitors

- ATN – within 1-2 weeks of treatment
- AIN
- Fanconi Syndrome
- Electrolyte Wasting
  - Phosphate
  - Sodium
  - Potassium
- Proteinuria

Proteasome Inhibitors

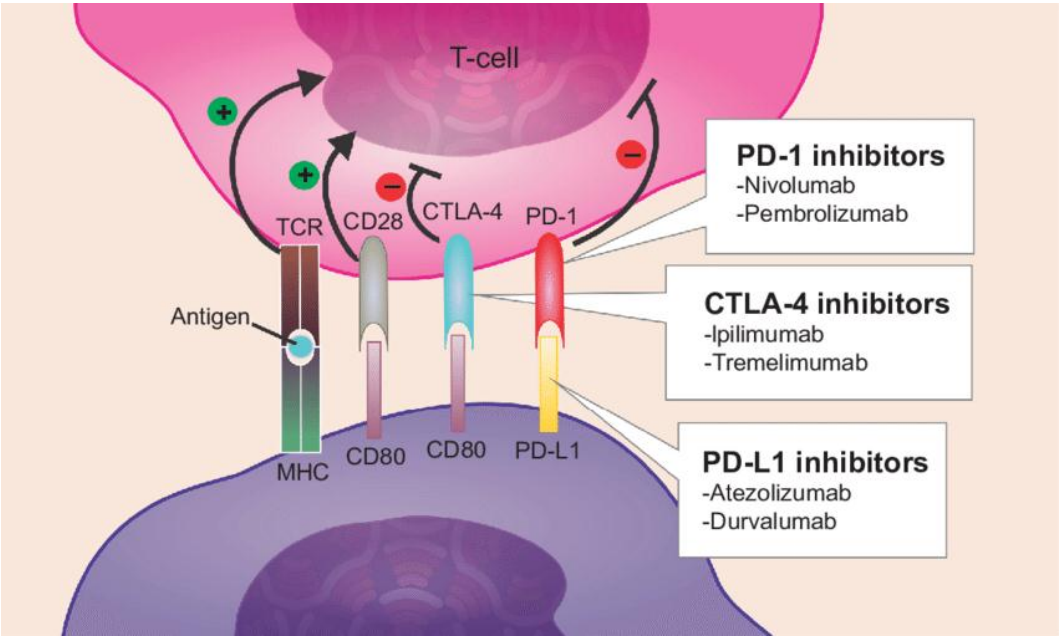
- Target the ubiquitin proteasome pathway
- Bortezomib, Carfilzomib
- Renal Adverse Events
  - Increased SCr – 24%
  - AKI – 5%
  - TMA

- Vasoconstriction of renal arteries proposed as mechanism for AKI.

- Decreased NF-κB levels in nucleus leads to decreased VEGF production as a mechanism for TMA.

Immune Checkpoint Inhibitors and AKI

- Associated with development of acute interstitial nephritis or granulomatous interstitial nephritis
- RRT needed in some patients
- Time course variable but can occur several weeks to months after starting therapy
- Steroids and drug withdrawal associated with recovery for majority



Cortazar et al. Kidney Int 2016; Shirali AS et al. AJKD 2016; Kidd J et al Kidney Int 2016

Immune Checkpoint Inhibitors

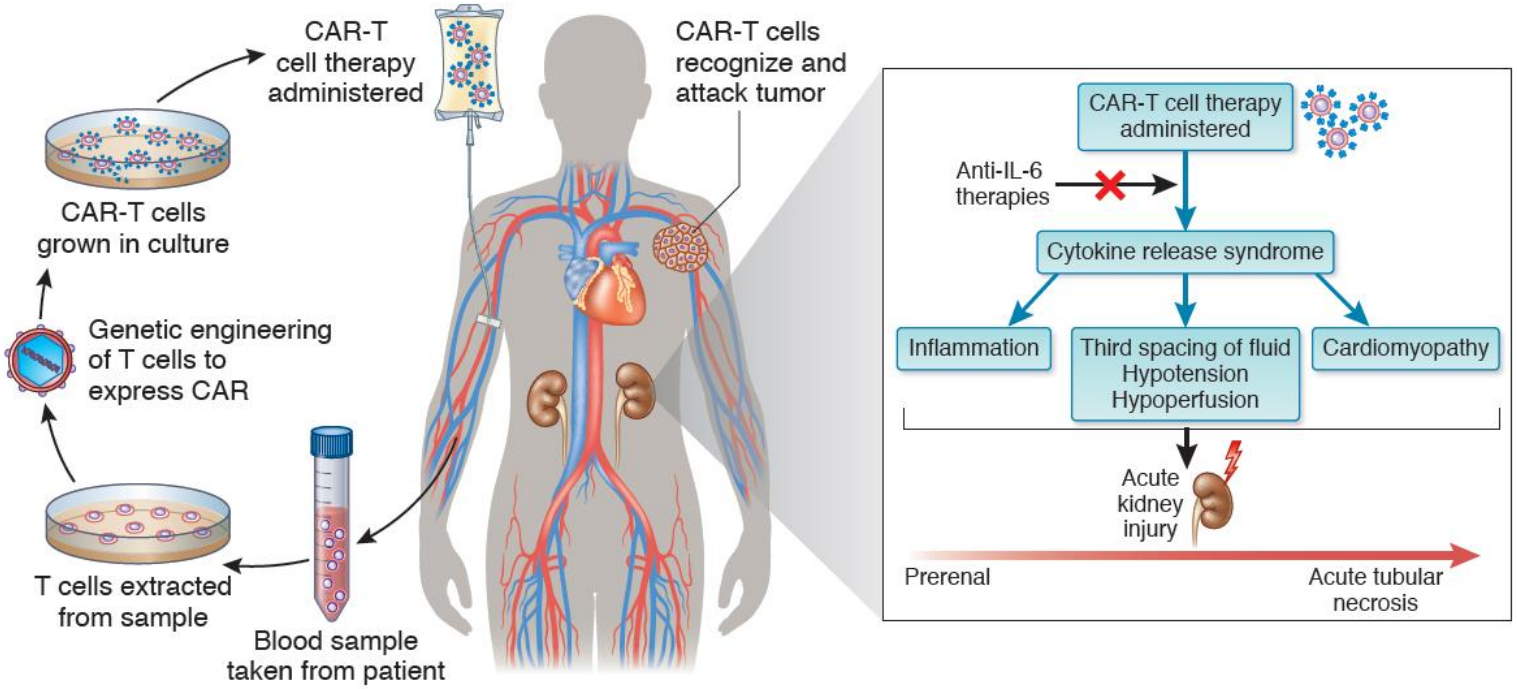
- Anti-CTLA-4 (cytotoxic T-lymphocyte antigen-4) targeted
  - Ipilimumab
- Anti-PD-1 (programmed cell death-protein 1) targeted
  - Nivolumab
  - Pembrolizumab
- Adverse events are due to augmented immune responses leading to autoimmune related inflammation
- Renal-related AEs
  - Elevated SCr
  - Autoimmune nephritis
  - Interstitial nephritis

Management of Renal Toxicity

Grade		Recommendation		
		Work-up	**Immunotherapy**	**Initial Treatment**
Grade 1	Serum creatinine 1–1.5 × baseline; > 1–1.5 × ULN, 1+ proteinuria or urinary protein < 1.0 g/24h	Monitor creatinie at least weekly	Continue	If creatinine worsens, treat as grade 2/3 or 4
Grade 2	Serum creatinine 1.5–3.0 × baseline; > 1.5–3.0 × ULN, 2+ proteinuria or 1.0–3.4 g/24h	Monitor creatinie at least every 2–3 days	Withold therapy and resume if symptoms are mild severity, resolve or return to baseline	(I) Administer methylprednisolone 0.5–1.0 mg/kg/day IV or equivalent and continue until improvement to mild severity. Taper over 1 month. (II) If creatinine increased >7 days or symptom worsen, treat as grade 4
Grade 3	Serum creatinine > 3.0 × baseline; > 3.0–6.0 × ULN, proteinuria >3.5 g/24h			
Grade 4	Serum creatinine 6.0 × ULN	(I) Monitor creatinine daily; (II) Consider nephrologist consultation with consideration of renal biopsy	Permanently discontinue	Administer methylprednisolone 1–2 mg/kg/day IV or equivalent and continue until improvement to mild severity. Taper over at least 1 month

Murakami N, et al., Curr Probl Cancer 2016.

CAR-T Cell Therapy and AKI



Jhaveri K and Rosner MH, CJASN 2018 in press

Prognosis of AKI

- Mortality rates of critically ill cancer patient with AKI are similar to general population and are very high.
- Recent study of AKI patients with cancer admitted to ICU:
  - ICU mortality: 55%
  - Hospital mortality: 64%
  - 6 month mortality: 73%
- In general, dialysis decisions should be guided by global severity and reversibility of the acute illness more than the specific cancer diagnosis unless the cancer is very advanced or pre-illness QoL was very poor.

Summary

- AKI is common in patients with cancer and has some unique features that require specific diagnostic and therapeutic approaches.
- Medications are a common etiology of AKI
- Decision making in patients with AKI and cancer can be very complex and is best done within a multi-disciplinary model with patient and family input.