Onco-Nephrology

Cytotoxic Drugs & the Kidney

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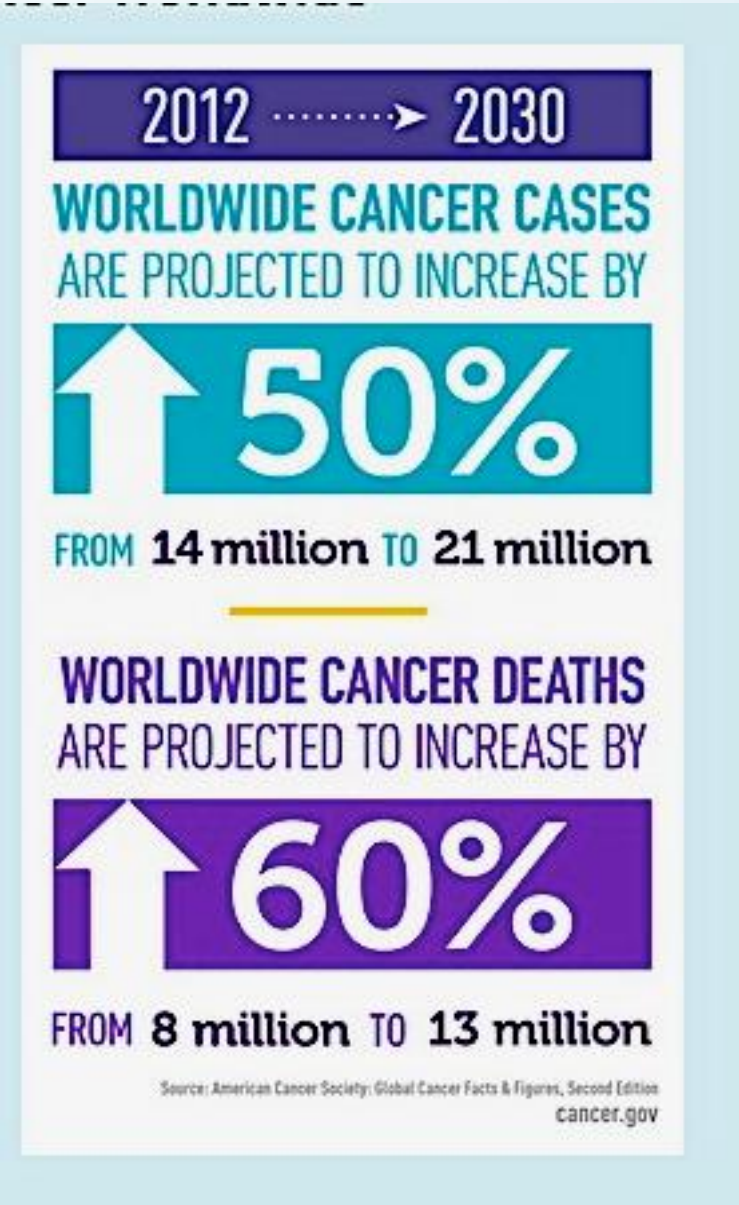
Cancer

A Common Global Problem

- Cancer is common and a leading cause of death worldwide
- Estimated 9.6 million deaths in 2018
- The most common causes of cancer death are the following:

- **LUNG (1.76 MILLION DEATHS)**
- **COLORECTAL (862,000 DEATHS)**
- **STOMACH (783,000 DEATHS)**
- **LIVER (782,000 DEATHS)**
- **BREAST (627,000 DEATHS)**



World Health Organization

Cancer and The Kidney

- The kidneys are a major elimination pathway for many antineoplastic drugs and their metabolites
- The kidney impairment can result in delayed drug excretion and metabolism of chemotherapeutic agents, and increased systemic toxicity
- Use of potentially nephrotoxic drugs in 80 percent of chemotherapy sessions

Renal complications associated with malignancy (cancer related vs. therapy related)

- **Paraneoplastic renal manifestation**
- **Need for nephrectomy and urinary tract obstruction**
- **Nephrotoxicity effects of chemotherapy:**
- Acute kidney disease (AKI)
- Toxic acute tubular necrosis
- Thrombotic microangiopathy (TMA)
- Crystal nephropathy
- Proteinuria/nephrotic syndrome due to TMA and glomerulopathies
- Electrolyte and acid-base disorders
- Chronic kidney disease (CKD) due to glomerulopathies or interstitial nephritis)

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AKI incidence

Denmark: among 1.2 M people there were 37,267 incident cancer patients between 1999-2006

- **One-year risk of AKI: 17.5%**

(RIFLE--R category)

- **Five-year risk of AKI: 27%**

(RIFLE--R category)

- **Highest risk among**
- kidney cancer(44%),
- liver cancer (33%)
- Myeloma (31.8%)

Christiansen CF, et al. Eur J Intern Med 2011

Anti-Cancer Agents

Conventional Agents

- Cytotoxic drugs (platins), Alkylating agents (ifosfamide)
- Antitumor antibiotics (mitomycin C)
- Antimetabolites (methotrexate, pemetrexed, pentostatin, gemcitabine, clofarabine)

Targeted agents

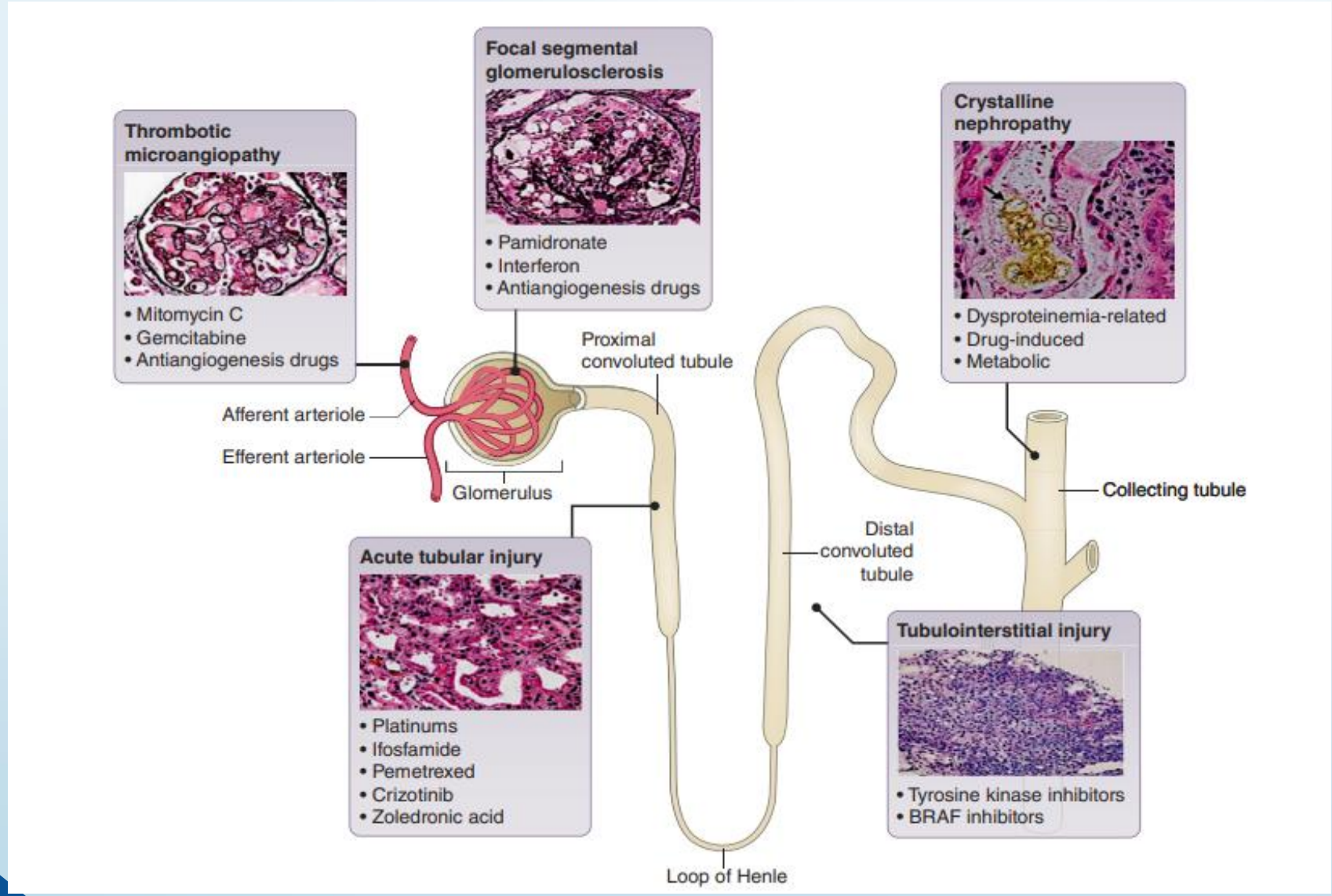
- Anti-angiogenesis drugs (anti-VEGF Ab, VEGF soluble receptors, TKIs)
- EGFR inhibitors, BRAF inhibitors, ALK inhibitors
- Proteosome inhibitors

Immunotherapies

- IL-2, interferon
- Immune checkpoint inhibitors (anti-CTLA-4, anti-PD-1, anti-PDL1)

Chimeric antigen receptor T cells

Anticancer therapies and their site of action in the nephron



Renal effects of anticancer drugs

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

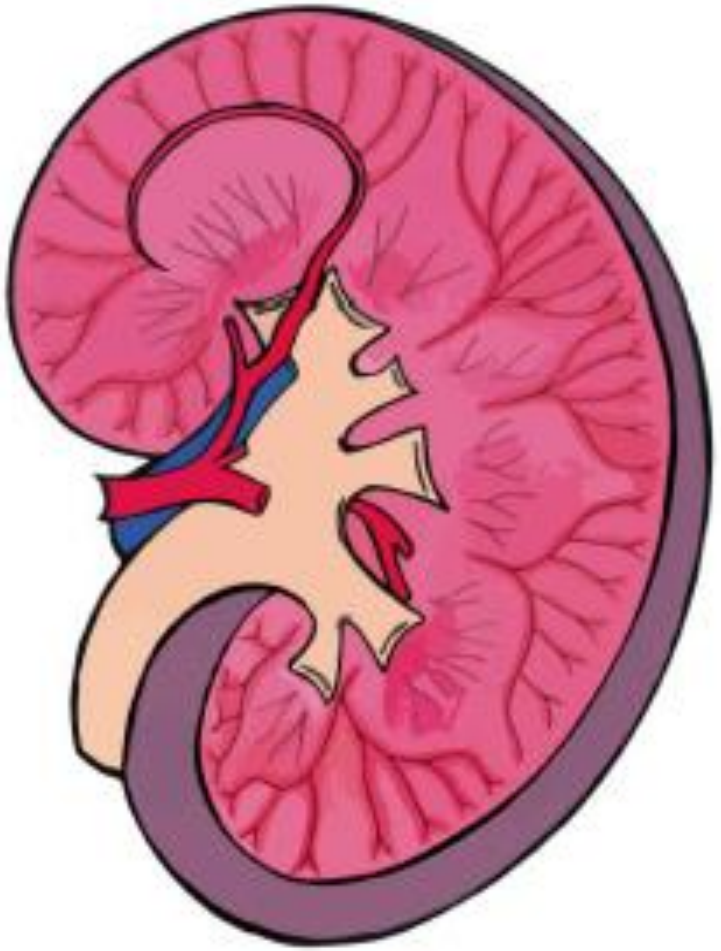


Table 1 Relationship between anticancer drug class, its nephrotoxic effects and mechanism of action of its lesion

Class	Drugs	Nephrotoxicity	Mechanism of action
Alkylating agents	Bendamustine; Cyclophosphamide; Ifosfamide; Melfalano; Nitrosureasnts	AKI; Hemorrhagic cystitis; Inflammatory lesion; SIADH; Hyponatremia; Fanconi's syndrome; Interstitial nephritis; Diabetes	Damage to proximal and distal tubular structures by action of metabolites and increased cellular oxidative stress
Antimetabolites	Chlopharabine; Methotrexate; Pemetrexed; Gemcitabine; Pentostatin	AKI; Decreased GFR; Interstitial edema; Tubular acidosis; Diabetes insipidus; Microangiopathic hemolytic anemia; SIADH; Hyponatremia	Decreased GFR due to vasoconstrictor action on afferent renal arteries; Crystal precipitation in tubules and induction of tubular injury
Anti-microtubular agents	Paclitaxis; Vincristine; Vinblastine; Vinorelbine	SIADH	Inhibits synthesis of genetic material or causes irreparable DNA damage
Antitumor antibiotics	Daunorubicin; Doxorubicin; Mitomycin	Nephrotic syndrome; Focal segmental glomerular sclerosis; TMA; AKI; Hemolytic uremic syndrome	Epithelial lesions (podocytes)
Platinum agents	Cisplatin; Carboplatin; Ocaliplatin	AKI; Anemia; Hypomagnesemia; Proximal tubular dysfunction; TMA	Drug accumulation in the proximal renal tubules
Cytotoxic agents	Arsenic trioxide; Etoposide; Irinotecan; Topotecan	Tubulointerstitial disease; Rhabdomyolysis; AKI	Increased exposure can be toxic; Higher levels of hematologic toxicity
Immunomodulatory drugs	Thalidomide; Lenalidomide; Pomalidomide	Hypercalcemia; Decreased GFR; Nephrolithiasis	Unclear, depending on the drug, may be related to its type of metabolism

Class	Drugs	Nephrotoxicity	Mechanism of action
Proteasome inhibitors	Bortezomib; Carfilzomib; Ixazomib	TMA; Acute interstitial nephritis; AKI	Prerenal causes (*e.g.*, hypovolemia); Tumor lysis-like syndrome
EGFR pathway inhibitors	Cetuximab; Panitumumab; Afatinib; Erlotinib; Gefitinib	Electrolyte disturbance; AKI; Diffuse proliferative glomerulonephritis; Nephrotic syndrome	Inhibition of EGFR signaling at the distal convoluted tubule, which regulates transepithelial magnesium transport; AKI mechanism is unclear, however, EGFR plays a role in the maintenance of tubular integrity
HER-2 inhibitors	Trastuzumab; Ado-trastuzumab emtansine; Pertuzumab	Proteinuria; AKI; Decreased GFR; Electrolyte disturbance; Hypertension	Unclear
BCL-2 inhibitors	Venetoclax; Obituzumab; Ofatumumab	AKI	Tumor lysis syndrome
ALK inhibitors	Crizotinib; Alectinib; Brigatinib	Decreased GFR; Development of complex renal cysts; Electrolyte disturbance	Unclear
BRAF inhibitors	Vemurafenib; Dabrafenib; Trametinib; Cobimetinib	Decrease GFR; AKI; Glomerulonephritis; Hyponatremia; Hypertension	Unclear
MTOR inhibitors	Temsirolimus	Glomerulopathy; AKI; Proteinuria	Unclear
BCR-ABL1 and KIT inhibitors	Bosutinib; Dasatinib; Imatinib	Hypophosphatemia; Decreased GFR; AKI; Proteinuria; Nephrotic syndrome; CKD	Rhabdomyolysis; Thrombotic thrombocytopenic purpura; Alterations in glomerular podocytes; Tumor lysis syndrome; Acute tubular injury

Class	Drugs	Nephrotoxicity	Mechanism of action
Anti-angiogenesis drugs (VEGF pathway inhibitors and TKI)	Bevacizumab; Ramucirumab; Aflibercept; Sunitinib; Sorafenib; Pazopanib; Ponatinib; Others	Hypertension; Proteinuria; Nephrotic syndrome; Decreased GFR; TMA; Glomerulopathy; Electrolyte disturbance	Endothelial cell dysfunction and dysregulation of podocyte
Inhibitor of Bruton's tyrosine kinase	Ibrutinib	AKI	Unclear, but tumor lysis syndrome might be contributory
Immune checkpoint inhibitors (PD-1, PD-L1, CTLA-4)	Ipilimumab; Pembrolizumab; Nivolumab	Acute tubulointerstitial nephritis; Immune complex glomerulonephritis; TMA; Electrolyte disturbance; AKI (rare)	Unclear, but development of autoantibodies that are pathogenic to the kidney might be contributory
Cytokine	INF-a	Proteinuria; Glomerulopathy; TMA; AKI	Minimal change disease or focal segmental glomerulosclerosis
Cytokine	IL-2	AKI	Capillary leak syndrome leading to AKI
Peptide receptor radioligand	Lutetium Lu-177 dotatate	Decreased GFR	Kidney irradiation

Renal complications associated with malignancy

Risk factors:

- Intravascular volume depletion
- The associated use of non-chemotherapeutic nephrotoxic drugs (analgesics, antibiotics,proton pump inhibitors and bone-targeted therapies)
- Radiographic ionic contrast media or radiation therapy
- Urinary tract obstruction
- Intrinsic renal disease
- These factors should be considered by the oncologist before initiating treatment to minimize the risk of nephrotoxicity

Renal complications associated with malignancy

Risk factors:

- Female gender
- Reduced muscle mass
- Reduced body water -mainly related to higher age
- Hypertension, diabetes, congestive heart failure, cirrhosis, hepatic failure, hyperbilirubinemia and hypoalbuminemia
- kidney-related risk factors: previous kidney injury, nephrotic syndrome and hydroelectrolytic disturbance which can be consequence of vomiting
- Diarrhea and use of diuretics

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Renal complications associated with malignancy

- The kidneys are major elimination pathway for many antineoplastic drugs and their metabolites
- kidney impairment can result in delayed drug excretion and metabolism of chemotherapeutic agents, and increased systemic toxicity
- Many drugs require **dose adjustment** when administered in the setting of kidney insufficiency

Renal complications associated with malignancy

Prevention of renal complications

Preventive strategies

Drug dose adjustment in patients with kidney impairment

- Based upon two factors: an estimation of GFR or creatinine clearance
- Evaluation of clinical signs of drug toxicity

(eg, neutropenia, thrombocytopenia)

Renal complications associated with malignancy

Estimation of kidney function

the most common methods used in routine clinical practice:

- Creatinine clearance calculation based upon a 24-hour collection of urine
- Cockcroft-Gault
- MDRD
- **CKD-EPI**

- In CKD patients, the current best approach for dosing chemotherapeutic agents is using the CKD-EPI equation

(Hydroxyurea could interfere with serum creatinine)

Renal complications associated with malignancy

For patients undergoing dialysis

- Dose reduction may be needed to avoid overexposure and drug toxicity

- Drug clearance by dialysis must be taken into account for appropriate timing of chemotherapy in patients treated with hemodialysis

(Partial dialysis removal may be used to improve drug tolerance such as cisplatin)

EXCRETING ANTI-CANCER DRUGS: SOME PHARMACOLOGY

- **Thinking about dosing**
- We tend to not think carefully about • Absorption, half-life, clearance, volume of distribution, etc, Metabolites
- We don’t have good ways to assess hepatic function
- We tend to be over-reliant on: Cockroft-Gault and MDRD equations
- **Thinking about renal function**
- eGFR > 60: “normal”
- eGFR 40-60: pretend its normal

  eGFR 10-40: look up dosing in some app or online
- eGFR<10 or dialysis

Conventional Cytotoxic Agents: Alkylating Agents

Cyclophosphamide

Toxicity caused by some of its metabolites

- In bone marrow and gonads
- Development of bladder cancer
- Hemorrhagic cystitis
- Hyponatremia

Alkylating Agents:Cyclophosphamide

Hyponatremia

Mechanism:

- Increased renal effect of antidiuretic hormone(SIADH)
- Chemotherapy induced nausea stimulation of ADH release
- Enhanced water intake fluid loaded to prevent hemorrhagic cystitis

Alkylating Agents:Cyclophosphamide

Hyponatremia

Usually seen in patients receiving

- high doses of intravenous (IV) cyclophosphamide (eg, 30 to 50 mg/kg or 6 g/m in the setting of hematopoietic stem cell transplantation)
- less common, with lower IV doses (eg, 10 to 15 mg/kg) given as pulse therapy or with oral therapy
- Hyponatremia typically occurs acutely and resolves within approximately 24 hours after discontinuation of the drug
- can be minimized by using isotonic saline

Alkylating Agents: Cyclophosphamide

Cyclophosphamide dose reduction in patients with kidney insufficiency?

- The United States Prescribing Information for cyclophosphamide states that patients with severe kidney impairment (CrCl = 10 - 24 mL/min)

They **do not recommend a specific dose reduction**, but do recommend that such patients be closely monitored for signs and symptoms of toxicity

- Cancer Care Ontario Guidelines suggest a **25 percent reduction in dose in patients with CrCl <50 mL/min** and use of extreme caution or drug discontinuation for CrCl <10 mL/min

Alkylating Agents:Cyclophosphamide

Cyclophosphamide in ESKD patients:

- Cyclophosphamide is moderately hemodialyzable

should be administered after hemodialysis

- In patients on peritoneal dialysis

Is suggest a 25 percent dose reduction

Alkylating Agents:Ifosfamide

Toxicity of ifosfamide

- Hemorrhagic cystitis
- SIADH

Affects the proximal tubule and acute tubular dysfunction(Fanconi's syndrome):

- Metabolic acidosis with a normal anion gap (hyperchloremic acidosis) due to type 1 (distal) or type 2 (proximal) renal tubular acidosis
- Hypophosphatemia induced by decreased proximal phosphate reabsorption, which can lead to rickets in children
- Renal glucosuria, aminoaciduria, and a marked increase in beta-2-macroglobulin excretion
- Polyuria due to nephrogenic diabetes insipidus

Hypokalemia

persistent decline in GFR over time

Alkylating Agents:Ifosfamide

Guidelines for dose reduction based upon kidney function

- Guidelines from Cancer Care Ontario recommend
- 25 percent dose reduction for CrCl 40 to 60 mL/min
- 50 percent dose reduction for CrCl 20 to 40 mL/min
- Drug be discontinued for CrCl <10 mL/min

Alkylating Agents

Hemorrhagic cystitis

- Most frequently described in patients receiving ifosfamide and Cyclophosphamide
- HC is a complex inflammatory response that is induced by a toxic metabolite (acrolein)

PREVENTION

forced saline diuresis

Mesna

For patients receiving daily ifosfamide at any dose or high-dose cyclophosphamide in the setting of hematopoietic cell transplantation (HCT)

intravenously (either continuous or bolus) or orally

Platinum Agents

Cisplatin

- One of the most commonly used antineoplastic drugs,
- One of the most nephrotoxic

Platinum Agents

Cisplatin is associated with:

- Acute kidney injury (AKI)
- Thrombotic microangiopathy (TMA)
- Hypomagnesemia
- Proximal tubular dysfunction (Fanconi-like syndrome)
- Anemia that is out of proportion to the drug's myelosuppressive effects

Platinum Agents

Carboplatin

- Is significantly less nephrotoxic than cisplatin
- Hypomagnesemia is the most common manifestation of nephrotoxicity
- AKI has been reported, particularly in patients previously treated with several courses of cisplatin
- Direct tubular injury leading to acute tubular necrosis is the primary mechanism

VEGF/VEGFR inhibitors

Bevacizumab

vascular endothelial growth factor (VEGF)

Is an anti-VEGF inhibiting antibody that functions by injuring renal vasculature and causing TMA and nephrotic syndroml

Produced by renal epithelial cells, VEGF signaling is essential for normal functioning of glomerular endothelial cells, mesangial cells, and peritubular capillaries

VEGF/VEGFR inhibitors

- Anti-VEGF therapy involves the inhibition of the nitric oxide (NO) pathway and oxidative stress, inducing endothelial cell dysfunction and vasoconstriction
- As a result of endothelial loss, glomerular injury and improper maintenance of a filtration barrier may develop with disrupted epithelial cell slit diaphragms and downregulation of nephrin evident on histopathology

VEGF/VEGFR inhibitors

Nephrotoxic effects of bevacizumab:

- New or worsening hypertension
- AKI and proteinuria
- Nephrotic syndrome

focal segmental glomerulosclerosis and membranous nephropathy