به نام خدایی که در این نزدیکی است

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ANTINEOPLASTIC AGENT &NSAIDS &ANIFUNGALS

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- One of the most fundamental aspects of kidney function is the elimination of endogenous and exogenous compounds.
- evaluation of excretory function is the cornerstone of assessing renal physiologic capacity.
- Excretion, by necessity, exposes the kidney to high concentrations of these substances; at high concentrations, these compounds and their metabolites can be toxic, causing injury or damage to the kidneys.

- There are two principal pathways for drug excretion by the kidney: glomerular filtration and tubular secretion.
- Glomerular filtration plays a major role with non-protein-bound small molecules (ie, of a size that can pass through the glomerular capillary wall).
- Such molecules cannot be filtered if they are protein bound in the circulation; these drugs, if they are renally excreted, enter the urine by secretion in the proximal tubule.

- For those drugs in which renal excretion is an important determinant of elimination of the intact drug or an active metabolite, dose adjustment is often required if kidney function is impaired.

- Although the prevalence of an elevated serum creatinine is low in cancer patients (<10 percent), the prevalence of a reduced glomerular filtration rate (GFR) is relatively high (50 to 53 percent in two cohort studies.

- Several factors can potentiate kidney dysfunction and contribute to the nephrotoxic potential of antineoplastic drugs These include:

- Intravascular volume depletion, either due to external losses or fluid sequestration (as in ascites or edema).
- This is one of the most common factors contributing to the nephrotoxic potential of antineoplastic drugs.

- The concomitant use of nonchemotherapeutic nephrotoxic drugs (eg, certain antibiotics [including aminoglycoside antibiotics], nonsteroidal anti-inflammatory agents, and proton pump inhibitors) or radiographic ionic contrast media in patients with or without preexisting kidney dysfunction.
- Urinary tract obstruction secondary to the underlying tumor.
- Intrinsic kidney disease that is idiopathic, related to other comorbidities, age related, or related to the cancer itself.

- Dose adjustment in this setting is typically based upon two factors: an estimation of glomerular filtration rate (GFR) or creatinine clearance (CrCl) that serves as an index of the number of functioning nephrons, and evaluation of clinical signs of drug toxicity (eg, neutropenia, thrombocytopenia).
- The available data in cancer patients suggest that most bedside formulae for estimating GFR or CrCl provide similar levels of concordance when used for the purpose of dosing renally excreted cancer drugs. In our view, estimates of GFR are preferred.

- Minimizing nonrenal systemic toxicity in patients receiving chemotherapy may be a particular problem in patients on chronic hemodialysis, especially when the details of drug elimination and metabolism are not fully known [11]. For patients undergoing dialysis, two issues must be considered :
- Since the kidneys are no longer functioning, 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.

- The following issues are pertinent to the dosing of carboplatin, which is uniquely based upon estimated GFR:
- For most patients, carboplatin dosing uses the Calvert formula, which is based upon desired exposure (area under the curve of concentration X time [AUC]) and GFR. When GFR is estimated based upon measured serum creatinine, we suggest limiting the maximal GFR to 125 mL/min for this calculation (**Grade 2C**). This suggestion does not apply if the GFR is directly measured.

DRUG HANDLING IN DIALYSIS PATIENTS

- Minimizing nonrenal systemic toxicity in patients receiving chemotherapy may be a particular problem in patients on chronic hemodialysis, especially when the details of drug elimination and metabolism are not fully known .For patients undergoing dialysis, two issues must be considered:
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- For those drugs in which a substantial fraction is removed by hemodialysis, chemotherapy should be administered after dialysis to avoid drug removal and loss of efficacy.
- On the other hand, for drugs that are not significantly removed by dialysis, administration is not related to the timing of dialysis.
- Partial dialysis removal may be used to improve drug tolerance. As an example, dialysis sessions may be started at a certain time following administration of a drug such as cisplatin to remove the drug that has not been distributed to its site of action but may still contribute to side effects.

ALKYLATING AGENTS

- **Cyclophosphamide** — The main urologic toxicity of cyclophosphamide is hemorrhagic cystitis. The primary renal effect of cyclophosphamide is hyponatremia, which is due to an increased effect of antidiuretic hormone (syndrome of inappropriate antidiuretic hormone secretion [SIADH]) impairing the kidney's ability to excrete water
- Chemotherapy-induced nausea may also play a contributory role since nausea is a potent stimulus to antidiuretic hormone release.

- Hyponatremia is usually seen in patients receiving high doses of intravenous (IV) cyclophosphamide (eg, 30 to 50 mg/kg or 6 g/m^2 in the setting of hematopoietic stem cell transplantation).
- Although less common, hyponatremia can also occur with oral therapy or with lower IV doses (eg, 10 to 15 mg/kg) given as pulse therapy in autoimmune diseases such as lupus nephritis.

- The combination of increased antidiuretic hormone effect and enhanced water intake can lead to severe, occasionally fatal hyponatremia within 24 hours.
- This complication can be minimized by using isotonic saline rather than hypotonic solutions to maintain a high urine output.
- However, hyponatremia can worsen even with isotonic saline administration.

- **Ifosfamide** — Similar to cyclophosphamide, the predominant toxicity of ifosfamide on the urinary tract is hemorrhagic cystitis. Ifosfamide can also cause SIADH.
- However, nephrotoxicity is more likely with ifosfamide than with cyclophosphamide.
- Ifosfamide nephrotoxicity affects the proximal tubule and is characterized by one or more of the following signs of acute tubular dysfunction:

- 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-microglobulin excretion, all from generalized proximal dysfunction
- Polyuria due to nephrogenic diabetes insipidus
- Hypokalemia, which may be severe, resulting from increased urinary potassium losses

- These data on tubular dysfunction come predominantly from pediatric patients treated with ifosfamide.
- Pre-existing kidney disease is a risk factor for ifosfamide nephrotoxicity.
- Guidelines for dose reduction based upon kidney function are available from expert groups, although they differ markedly.

ANTIMETABOLITES

- The elimination of many antimetabolites, including capecitabine, methotrexate, fludarabine, and pentostatin, is at least partially dependent upon kidney function.
- Of the clinically useful antimetabolites, only methotrexate is associated with significant kidney toxicity.

METHOTREXATE

- Methotrexate at doses less than 0.5 to 1 g/m^2 is usually not associated with kidney toxicity unless underlying kidney dysfunction is present.
- By contrast, high-dose intravenous methotrexate (1 to 15 g/m^2) can precipitate in the tubules and induce tubular injury; at particular risk are patients who are volume depleted and those who excrete acidic urine.
- Maintenance of adequate urinary output and alkalinization will lessen the probability of methotrexate precipitation.

- Methotrexate can also produce a transient decrease in GFR, with complete recovery within six to eight hours of discontinuing the drug.
- The mechanism responsible for this functional kidney impairment involves afferent arteriolar constriction or mesangial cell constriction that produces reduced glomerular capillary surface area and diminished glomerular capillary perfusion and pressure [71].
- Methotrexate has also been associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

ANTITUMOR ANTIBIOTICS

- **Anthracyclines and related agents** — Anthracyclines such as daunorubicin and doxorubicin have been known to cause nephrotic syndrome with kidney lesions consistent with minimal change disease, focal segmental glomerular sclerosis not otherwise specified (NOS), or collapsing glomerulopathy.
- In addition, pegylated liposomal doxorubicin has been associated with renal thrombotic microangiopathy, nephrotic syndrome, and acute kidney injury.

PLATINUM AGENTS

- **Cisplatin** — Cisplatin is one of the most commonly used antineoplastic drugs, and it is also one of the most nephrotoxic. Cisplatin is associated with acute kidney injury (AKI), thrombotic microangiopathy (TMA), hypomagnesemia, proximal tubular dysfunction (ie, Fanconi-like syndrome), and anemia that is out of proportion to the drug's myelosuppressive effects.
- Hydration is essential for all patients to prevent cisplatin-induced nephrotoxicity.
- The optimal approach to cisplatin therapy in patients with pre-existing kidney impairment or persistent kidney impairment during therapy is unknown.

- Clinical trial protocols often require a serum creatinine of less administration of the full dose of cisplatin, and they exclude patients with more significant kidney impairment [109].
- This restriction is probably related more to concerns regarding increased nonrenal toxicity (ototoxicity, neuropathy) than to an increased risk of AKI.
- The United States Prescribing Information for cisplatin recommends that repeat courses of cisplatin not be given unless or until serum creatinine is <1.5 mg/dL and/or blood urea nitrogen (BUN) is <25 mg/dL; there are no suggested renal dose adjustment guidelines.

- Although the available data are scant and predominantly comprised of single case reports, cisplatin-containing chemotherapy combinations have been successfully administered to patients undergoing hemodialysis [12,110-112].
- One guideline suggests that such patients have a 50 to 75 percent reduction in dose and that the drug be administered after hemodialysis [12].
- A 50 percent dose reduction is also recommended for patients undergoing peritoneal dialysis.

- **Carboplatin** — In both experimental and clinical studies, carboplatin is significantly less nephrotoxic than cisplatin. Hypomagnesemia appears to be the most common manifestation of nephrotoxicity, although it occurs less often than with cisplatin.

- A renewed interest in mycology has spurned an increase in Amanita phalloides (poison mushroom) ingestion with most cases being accidental due to misidentification [58].
- These plant toxins, once ingested, cause cellular apoptosis, necrosis, and microvascular thrombosis.
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NSAID

- While the primary phenotype of NSAID nephrotoxicity is AKI, disruption of homeostatic physiology can lead to electrolyte disturbances (hyperkalemia or hyponatremia), edema, and papillary necrosis.
- It is likely that the nonspecific nature of COX blockade and the resultant interference with prostaglandin synthesis is primarily responsible for the nephrotoxicity of NSAIDs.

- The prostaglandins PGE2 and PGI2 are responsible for renal vasodilatation, which increases renal blood flow and GFR.
- Disruption of this vasodilatory process becomes more clinically apparent in scenarios where renal perfusion is already compromised (e.g., heart failure, intravascular volume depletion, sepsis) or in cases where vasoconstricting hormones, such as angiotensin II, are also upregulated (e.g., concomitant administration of ACE inhibitors)
- in these cases, NSAID administration may lead to a substantial decrease in GFR and overt AKI.

- While NSAIDs can be used safely when attention is paid to their potential for nephrotoxic risk, AKI occurs in up to 5% of patients receiving these agents;
- this risk may be exacerbated by any sort of intravascular volume depletion as described above, as well as in the setting of reduced GFR or CKD.
- In the setting of severe dehydration or massive overdose NSAIDs can even cause acute renal papillary necrosis.

- The vascular blood supply in the renal papillae is highly dependent on prostaglandin production and impaired production can cause ischemia.
- Clinically, these patients may present with abdominal or flank pain and gross hematuria.
- While renal function may return to baseline, maximal concentration of the urine may be impaired due to the loss of the deep loops of Henle

- Prostaglandins modulate sodium and water handling and NSAIDs use can lead to water and sodium retention [155].
- This effect is particularly pronounced in patients with preexisting positive sodium and water balance such as those in heart failure or with nephrotic syndrome.
- Hyperkalemia is uncommonly seen with NSAID use unless other agents prone to cause potassium retention are administered concomitantly (e.g., potassiumsparing diuretics, potassium supplements, ACE inhibitors, or trimethoprim therapy)

- Finally, NSAIDs can lead to AIN which may present similarly to AKI. However, patients with AIN are more likely to have systemic symptoms including fever, joint or abdominal pain, and rash [22].
- While sterile leukocyturia may be present, this is not a ubiquitous finding and definitive diagnosis requires a kidney biopsy.
- Distinguishing between AKI and AIN is important as management between the conditions may differ.


با تشکر از توجه شما