Nephrotoxicity of Chemotherapeutic Agents

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Introduction

- Despite positive advancement in chemotherapeutics for various malignancies, drug nephrotoxicity remains a complication and sometimes limits life-saving therapy
- The relationship of nephrologists and oncologists in the care of these patients has given rise to growing area of Onco-Nephrology.

Risk for kidney injury

- Nearly 60% of patients with cancer have some form of renal disease
- Direct malignant effects include :
- myeloma-related kidney injury, infiltration of the renal parenchyma as seen with leukemias and lymphomas
- urinary tract obstruction from various cancers, and secondary glomerulopathies

Risk for kidney injury

- Indirect effects include :
- Effective volume depletion from nausea/vomiting, diarrhea, overdiuresis, malignant ascites or pleural effusions, sepsis, and cardiac involvement, which sensitizes the kidney to nephrotoxins by inducing a prerenal state
- metabolic disturbances such as hyperuricemia and hypercalcemia,hypergycemia.

Risk for kidney injury

- Combined exposure of chemotherapeutic agents with other nephrotoxins will raise the risk for kidney injury
- High doses and prolonged chemotherapy increase the chance of renal injury
- unrecognized depressed GFR, higher rates of renal oxidative stress, and excessive levels of angiotensin-II/endothelin, all of which increase drug nephrotoxicity.

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

Kidney injury associated with chemotherapeutic agents

- 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 diseaseand focal segmental glomerulosclerosis:
- IFN
- pamidronate
- zoledronate (rare)

Kidney injury associated with chemotherapeutic agents

- Tubulointerstitium:
- acute tubular necrosis :platinums, zoledronate, ifosfamide, and mithramycin pentostatin, imatinib, diaziquone, and pemetrexed

- tubulopathies
- Fanconi syndrome :cisplatin, ifosfamide, azacitadine, diaziquone, imatinib, and pemetrexed

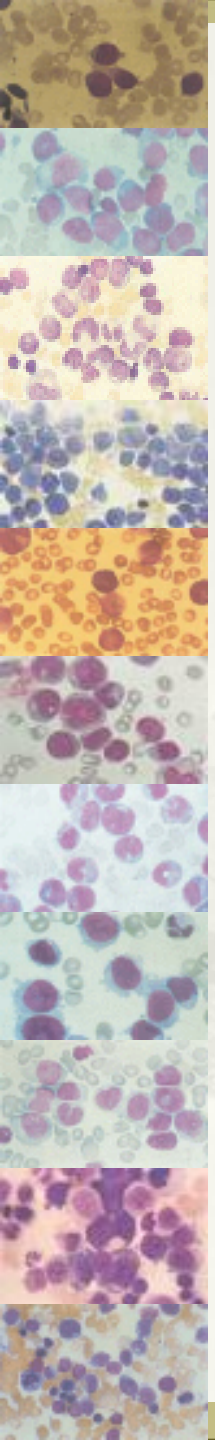
- salt wasting :cisplatin and azacitadine

Kidney injury associated with chemotherapeutic agents

- Magnesium wasting:cisplatin, cetuximab, and panitumumab
- Nephrogenic diabetes insipidus :cisplatin, ifosfamide, and pemetrexed
- syndrome of inappropriate antidiuresis: cyclophosphamide and vincristine
- acute interstitial nephritis :sorafenib and sunitinib
- crystal nephropathy :methotrexate

MTX toxicity

- Acute MTX toxicity presents as pancytopenia, gastrointestinal (GI) mucositis, hepatotoxicity, pulmonary toxicity, and acute renal failure



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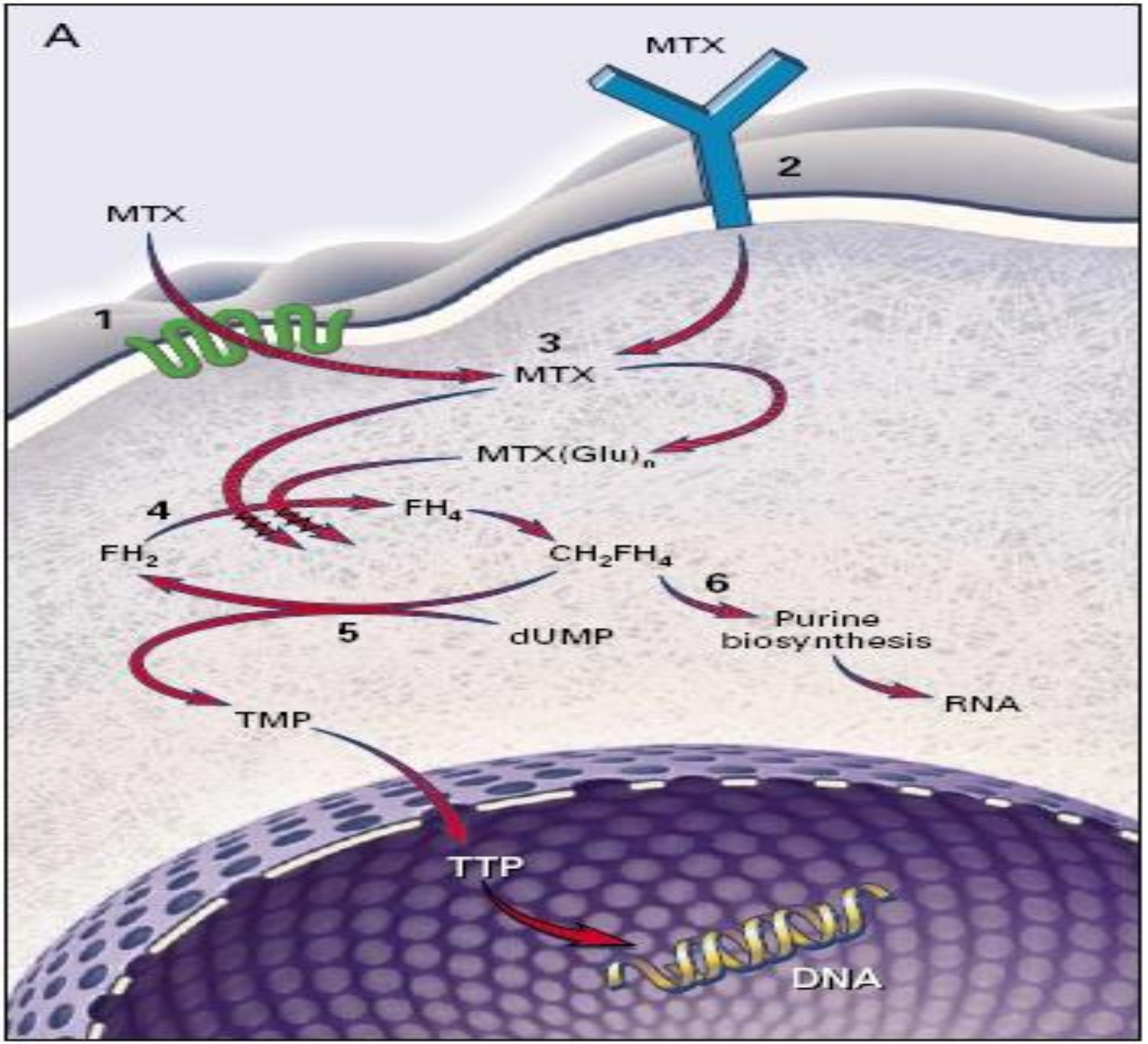
A
MTX
2
MTX
1
3
MTX
MTX(Glu)n
4
FH4
FH2
CH2FH4
6
5
dUMP
Purine
biosynthesis
RNA
TMP
TTP
DNA

MTX toxicity

- MTX inhibits dihydrofolate (DHF) reductase, an enzyme responsible for the conversion of DHF to tetrahydrofolate (THF).
- Consequently, there is a reduction in thymidylate and purine biosynthesis.
- DNA synthesis eventually halts and cells can no longer divide.

MTX toxicity

- Major toxic effects of MTX, such as hepatic, GI mucosa ,renal, pulmonary, and bone marrow disorders, may be life-threatening.
- MTX-induced nephrotoxicity mainly arises by two mechanisms: Crystal nephropathy and direct tubular toxicity.
- Glomerular filtration, tubular secretion, and tubular reabsorption all play a role in the renal clearance of MTX.
- Paradoxically, toxic levels of MTX pose a grave danger to renal tubules thereby leading to decreased renal clearance.

MTX toxicity

- Prolonged renal dysfunction with increased systemic methotrexate exposure can cause myelosuppression, mucositis, hepatotoxicity, and, in severe cases, multiorgan failure

Predisposing factors for developing MTX toxicity

- Acute renal failure, hypoalbuminemia, and concurrent use of drugs known to interact with MTX.
- Salicylates and nonsteroidal anti-inflammatory drugs (NSAIDs) can decrease the renal elimination and the tubular secretion of MTX
- Trimethoprim/sulfamethoxazole (Septran ®) can enhance the cytotoxic effects of MTX as trimethoprim is an antifolate reductase inhibitor.
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Predisposing factors for developing MTX toxicity

- pre-existing nephropathy because of previous drug toxicity (e.g., from cisplatin)
- Associated disease, metabolic derangements due to the presence of tumor, advanced age, Pharmacogenetic factors (such as hyperhomocysteinemia with concurrent relative or absolute folate deficiency)
- Delayed methotrexate excretion has been associated with extravascular fluid collections, including ascites, pleural effusions, or intracranial fluid

Methotrexate

- *At low doses it is not usually associated with renal toxicity but may be seen.*
- *However with high doses, nephrotoxicity can occur significantly- 60% in one report.*

Methotrexate

- *Methotrexate is renally excreted. At lower pH, it precipitates and causes tubular injury.*
- *Pts who are dehydrated and excrete acidic urine are especially at risk.*
- *Extensive necrosis of the epithelium of the convuluted tubules has been seen.*

Preventing and Managing Toxicities of High-Dose Methotrexate

- *Close Monitoring: Urine output, Fluid Balance (avoid negative balance) MTX levels, Serum Cr.*
- *IV hydration and urinary* ***alkalinizations are mainstays in prevention.***
- *Leucovorin* •
- Glucarbidase cleaves methotrexate to noncytotoxic metabolites.
- It is reserved for use when methotrexate levels are toxic, and there is significant risk for systemic toxicity
- High-flux hemodialysis

IV hydration

- Many pediatric protocols recommend at least 2 hours of hyperhydration of a minimum of 200 mL/m^2 per hour or 100–150 mL/m^2 per hour beginning 12 hours before the start of methotrexate infusion and continuing for 24–48 hours or longer if the patient has a history of methotrexate toxicity or develops delayed methotrexate elimination

Urinary alkalinizations

- administration of fluids with 40 mEq/L sodium bicarbonate is recommended during and after HDMTX administration .
- A urine pH of 7 or greater should be required before administration of methotrexate to reduce crystal formation.
- It is also important to check urine pH values with each void during the infusion to ensure no extended periods of time with acidic urine

In patients with serum alkalosis and inadequate urine alkalinization

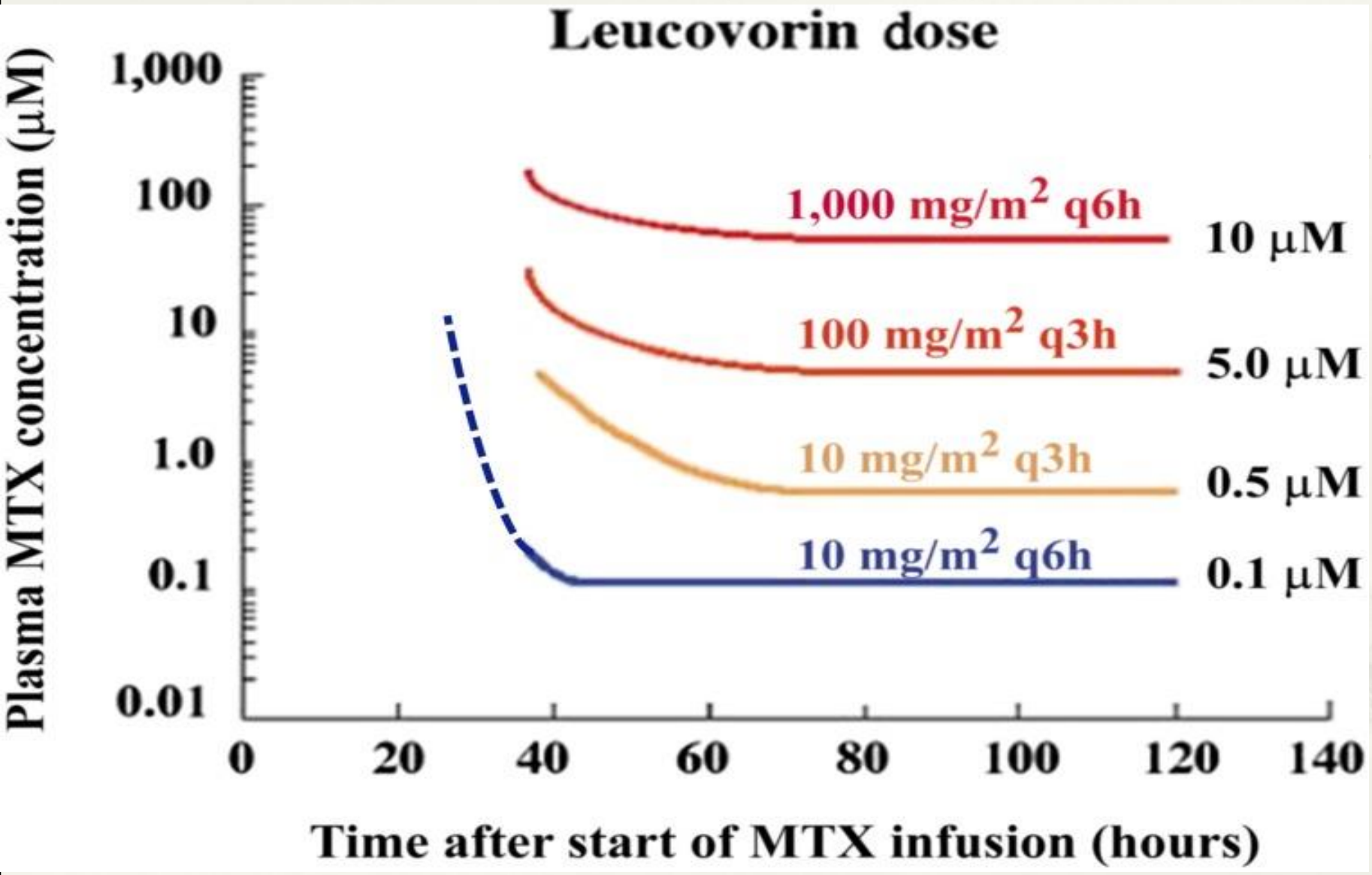
- The ***carbonic anhydrase inhibitor*** acetazolamide (250–500 mg p.o. four times daily) may be added to directly alkalinize the urine by increasing renal excretion of sodium, water, and bicarbonate, without increasing serum pH

Leucovorin

- Is particularly effective in the prevention of myelosuppression, gastrointestinal toxicity, and neurotoxicity during treatment with HDMTX
- Because leucovorin effectively neutralizes the effects of methotrexate, it must not be started too early because it would then reduce not only toxicity but also anticancer efficacy.

Leucovorin

- Serum methotrexate concentrations should be monitored with ongoing adjustments in hydration, alkalinization, and leucovorin rescue until the target of less than 0.05–0.1 μM is reached
- in centers where methotrexate levels cannot be monitored, assiduous monitoring of urine pH and output, serum creatinine, and twice-daily examination of mucosal membranes for evidence of inflammation can allow safe administration of HDMTX for most patients


Leucovorin dose
Plasma MTX concentration (μM)
1,000
100
10
1.0
0.1
0.01
0
20
40
60
80
100
120
140
Time after start of MTX infusion (hours)
1,000 mg/m2 q6h
100 mg/m2 q3h
10 mg/m2 q3h
10 mg/m2 q6h
10 μM
5.0 μM
0.5 μM
0.1 μM

Extracorporeal techniques

- retrospective analyses of differing approaches without control groups, including plasmapheresis, charcoal hemoperfusion, high-flux hemodialysis, conventional hemodialysis, and peritoneal dialysis make it difficult to identify one optimal extracorporeal strategy.

Extracorporeal techniques

- High-flux hemodialysis is likely to be the most effective based on technique and flow rates and reduced methotrexate concentrations during a 6-hour period in one series, whereas peritoneal dialysis is unlikely to be effective
- Leucovorin is removed by dialysis, and so it should be redosed afterward

Glucarpidase

- Glucarpidase cleaves methotrexate into DAMPA and glutamate, two nontoxic metabolites, and thus provides an enzymatic method to rapidly remove methotrexate in patients with renal dysfunction
- A single dose of glucarpidase (50 U/kg i.v. over 5 minutes) reduces plasma methotrexate concentrations by 97% or more within 15 minutes
- it has no effect on intracellular methotrexate concentrations

Glucarpidase

- after glucarpidase administration, leucovorin should be continued until methotrexate concentrations have been maintained at close to undetectable levels for several more days.
- Leucovorin should not be administered within 2 hours before or after a dose of glucarpidase because, like methotrexate, leucovorin is a substrate for glucarpidase.

Glucarpidase

- Within 48 hours of glucarpidase administration, only a chromatographic method can reliably measure methotrexate concentrations because the DAMPA produced by enzymatic breakdown of methotrexate cross-reacts with methotrexate in the standard immunoassay and artificially elevates the level .

Thymidine

- Thymidine was restricted to patients with prolonged methotrexate exposure (>96 hours) or with substantial methotrexate toxicity.

Dose modification of MTX based on GFR :

- *GFR (ml/min) >80 DOSE 100%*
- *GFR (ml/min) > 60 dose 65%*
- *GFR (ml/min) > 45 dose 50 %*
- *if GFR <30 Contra Indicated*

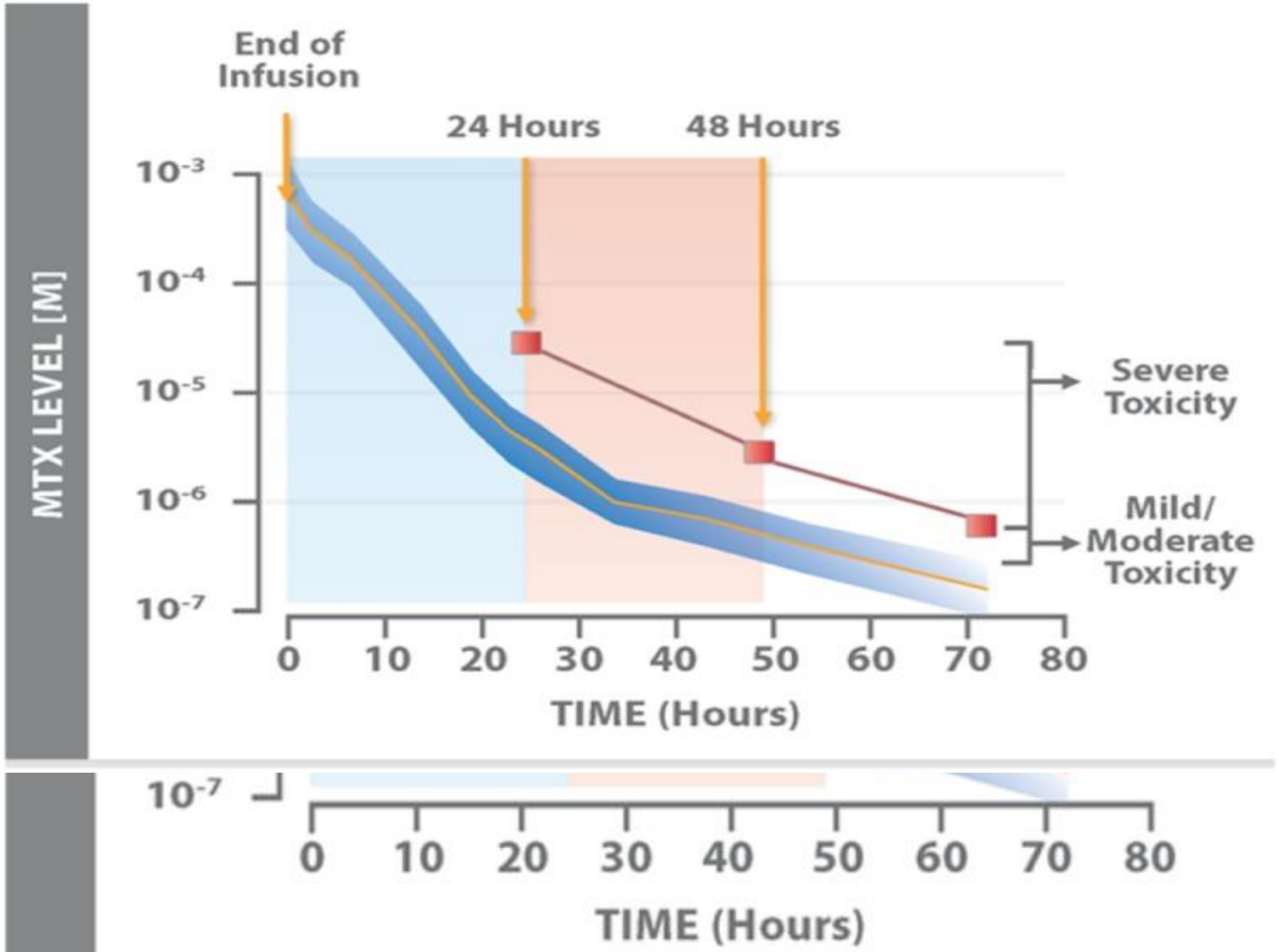
General Measures to Prevent Drug-Induced N ephrotoxicity

- Adjust medication dosages using the Cockcroft-Gault formula (in adults) or Schwartz formula (in children).
- Assess baseline renal function using the MDRD equation, and consider patient's renal function when prescribing a new drug.

General Measures to Prevent Drug-Induced N ephrotoxicity

- Avoid nephrotoxic combinations.
- Correct risk factors for nephrotoxicity before initiation of drug therapy.
- Ensure adequate hydration before and during therapy with potential nephrotoxins.
- Use equally effective non-nephrotoxic drugs whenever possible.

Thanks


End of Infusion
24 Hours
48 Hours
MTX LEVEL [M]
10-3
10-4
10-5
10-6
10-7
Severe Toxicity
Mild/ Moderate Toxicity
0 10 20 30 40 50 60 70 80
TIME (Hours)

10-7
0 10 20 30 40 50 60 70 80
TIME (Hours)

Cisplatin

- ***Nephrotoxicity Profile:-***
- ☐ *Primarily injures the S3 segment of the proximal tubule.*
- ☐ *Tubular injury also stimulate inflammatory response causing further damage.*
- ☐ *Also induces vasoconstriction in the renal vasculature thus reducing renal blood flow and causing ischemic injury.*
- ☐ *It is usually dose dependent.*

Clinical Features

- *• Clinically, Nephrotoxicity is seen usually within 10 days of Cisplatin administration.*
- *• It is manifested by acute renal failure, hypokalemia , hypomagnesemiaand Fanconi like syndrome.*
- *• Hypomagnesemia may exacerbate Cisplatin toxicity.*

Clinical Features

- ☐ *Proximal tubular dysfunction is the most common presentation which could lead to Fanconi's syndrome, hypophosphatemic rickets and proximal renal tubular acidosis.*
- ☐ *Chronic progressive toxicity has been reported and long term evaluation in children is needed.*

- • *UOP typically remains above 1 liter/day (unless renal dysfunction is severe) due to induction of a concentrating defect, due to platinum*
- *induced damage to the loop of henle or decrease in aquaporin water channels in collecting tubules.*
- *cisplatin treatment may lead to long term reduction in GFR as well.*
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Prevention

- • *Lower doses of cisplatin*
- ☐ *Administration of intravenous saline.*
- ☐ *Sodium thiosulphate- binds to cisplatin and render it non-toxic.*
- ☐ *Amifostine: an organic thiophosphate, donates a thiol group selectively in normal tissues and not in malignant tissues, to bind to cisplatin.*

- *Major concerns are cost and possible interference with tumor efficacy.*
- ☐ *Cimetidine-inhibitor of OCTs- could be used to decrease uptake.*
- *Imatinib, an anti-cancer agents also decreases uptake by affecting OCTs.*
- ☐ *Antioxidants have been tried-unclear benefit.*
- ☐ *Other agents that have been explored include N-acetylcysteine, theophylline,glycine etc*

Carboplatin

- ***Nephrotoxicity Profile:-***
- ☐ *Acute renal failure has been reported with carboplatin.*
- ☐ *Biopsy specimens showed focal and moderate interstitial nephritis with periglomerular fibrosis in one specimen and edematous interstitium with diffuse mononuclear infiltrate and toxic changes in tubules in the other.*

Clinical Features

- ☐ *Decrease in GFR has been noted in children after treatment with carboplatin.*
- *Direct tubular injury seems to be the mechanism and is dose dependent.*
- ☐ *Hypomagnesemia is a more common side effect.*
- ☐ *Renal salt wasting has also been reported.*
- ☐ *Careful monitoring of renal function is warranted.*

Cyclophosphamide

- ☐ ***Nephrotoxicity Profile:-***
- ☐ *Major toxicity of cyclophosphamide is hemorrhagic cystitis.*
- ☐ *SIADH (syndrome of inappropriate antidiuretic hormone secretion)*
- ☐ *Nephrogenic diabetes insipidus*
- ☐ *One of the metabolites acrolein causes cystitis*

- *Clinical Features*
- ☐ *Hyponatremia has also been reported.*
- *Mechanism could be increased ADH or a direct effect on the kidney resulting in enhanced permeability of distal tubules to water.*
- ☐ *Water retention is usually acute and resolves within 24 hrs of withdrawal of drug.*

Prevention

- ☐ *Hypotonic solutions should be avoided while giving cyclophosphamide to prevent severe hyponatremia.*
- ☐ *Mesna and IV hydration are mainly used for prevention.*
- ☐ *Mesna contains a sulfhydryl group that binds acrolein and detoxifies it.*
- *IV hydration induces brisk diuresis and prevents accumulation of acrolein in the urinary bladder and collecting system*

Ifosfamide

- ***Nephrotoxicity Profile:-***
- ☐ *Nephrotoxicity is more prominent feature especially when given along with other nephrotoxic agents like Cisplatin.*
- ☐ *Fanconi syndrome, CKD, SIADH, Nephrogenic diabetes insipidus; risk factors include cumulative ifosfamide dose . 50 g/m2, preexisting GFR loss and/or nephrectomy, age # 12 y*

Clinical Features

- ☐ Proximal tubular dysfunction is the most common presentation which could lead to Fanconi's syndrome, hypophosphatemic rickets and proximal renal tubular acidosis.
- ☐ Chronic progressive toxicity has been reported and long term evaluation in children is needed.

Prevention

- ☐ *If possible, ifosfamide should be discontinued in patients developing signs of moderate to severe AKI during therapy.*
- ☐ *oral and/or IV fluid and electrolyte supportive therapy should be provided*
- *Mesna can be given for prevention.*

Nitrosoureas

- ***Carmustine, Semustine ,Lomustine and Streptozocin.***
- ☐ *Used for malignant brain tumors,melanomas.*
- ☐ *Of the four agents, Semustine and Streptozocin are more nephrotoxic.*

- ***Nephrotoxicity Profile:-***
- ☐ *Fanconi syndrome, CKD, glomerular toxicity, kidney failure*
- ☐ *They induce chronic interstitial nephritis which is slowly progressive and irreversible.*
- ☐ *Glomerular sclerosis and interstitial fibrosis has been seen.*

* Clinical Features
* ☐ Mild proteinuria or an asymptomatic elevation of creatinine is usually the first sign of renal involvement.
* ☐ Onset of clinical nephrotoxicity may be delayed up to months to years after last dose.
* ☐ Careful follow up is essential.

Prevention

- ☐ *Administration of supplemental crystalloid fluid; reduction of the carmustine infusion rate by 50%*

- ☐ *Discontinuation of the drug (continued treatment generally results in irreversible injury)*

Gemcitabine

- ☐ *Renal failure and microagiopathic hemolytic anemia has been associated.*
- ☐ *Incidence lesser than mitomycin C. Approximately 0.008%-0.078% .*
- ☐ *Interval from the last dose of gemcitabine to development of HUS ranged from 1 day to several months.*

Prevention:

- *Immunosuppressive therapies (azathioprine, corticosteroids or vincristine), and antiplatelet/anticoagulant therapies(heparin, prostacyclin or splenectomy)*
- ☐ *If the drug is still being given when gemcitabine-associated TMA is identified, it must be discontinued*
- *Withdrawal of drug, steroids and plasmapheresis have been tried with variable response*

Mitomycin C

- *Most common form of nephrotoxicity is renal failure and microangiopathic hemolytic anemia.*
- ☐ *Most likely occurs after 6 months of therapy.*
- ☐ *It is believed that direct endothelial injury is the inciting event.*
- *fibrin deposition in the small renal arterioles.*
- ☐ *Dose dependent.*

Clinical Features

- *slowly progressive renal failure and hypertension.*
- ☐ *Patients may have bland urine sediment or may present with hematuria and proteinuria.*
- ☐ *Non-cardiogenic pulmonary edema may be seen.*
- *Renal failure may respond to plasmapheresis*

Prevention:-

- ☐ *Prompt diagnosis*
- ☐ *Early discontinuation of the drug,*
- ☐ *Supportive treatment may improve the outcome*

Thanks

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