High dose methotrexate (HDMTX): doses ≥ 500mg/m² IV

MOA: folate antagonist; inhibits dihydrofolate reductase (DHFR), thymidylate and alters transport of reduced folates

Metabolism: liver and intracellular metabolism to active metabolites

Distribution: kidney, gallbladder, spleen, liver and skin; HDMTX required to promote diffusion across the blood brain barrier; accumulates in third space fluids

Excretion: ~90% in the urine via glomerular filtration and active tubular secretion

Defining the risks of HDMTX:

Cmax = efficacy vs. AUC = toxicity

Renal dysfunction (direct tubular injury; transient reduction in GFR) → prolonged exposure → increased gastrointestinal (e.g. mucositis, nausea), marrow, neurologic, dermatologic and hepatic toxicities

Who is at risk?

Patient factors include:
- Advanced age
- Reduced renal function
- History of previous toxicities with Methotrexate or nephrotoxic drugs
- Extravascular fluid collections → prolonged clearance due to slow diffusion
- Pharmacogenetics explains, in part, interpatient variability, efficacy, toxicities

Protocol factors include:
- Higher doses → higher risk of toxicities
- Dose adjustment → no clear guidance for renal dysfunction (chronic, acute)
- Infusion time: longer infusion time delays start of leucovorin → increased toxicity
- Supportive measures and medications used to prevent and minimize toxicities

Drug interactions (non-exhaustive list):
- Compete for renal tubular secretion: penicillin and derivatives, NSAIDs, salicylates, Sepruta, probenecid, gemfibrozil
- Reduce renal transport/clearance: proton pump inhibitors
- Compete for binding sites on the DHFR molecule: Trimethoprim
- Decrease plasma protein binding: salicylates e.g. ASA
- Increase myelosuppression: thiazide diuretics
- Drugs with additive nephrotoxic effects: aminoglycosides, amphotericin etc.

Dosing Adjustments:

Arnoff
- CrCl 10-50 mL/min = 50%
- CrCl ≤10 mL/min = avoid
- Hemodialysis/CRRT = 50% (vs.25%) post HD

Kintzel et al.
- CrCl >80 mL/min = 100%
- CrCl 65 mL/min = 60%
- CrCl 45 mL/min = 50%

Other: BCCA
- CrCl ≥100 mL/min = 100%
- CrCl 85 mL/min = 85%
- CrCl 60 mL/min = 60%

*HDMTX given only if CrCl > 60 mL/min.

Supportive Care:

Hyper hydration:
- Start before (up to 12 hrs)
- Adults: 150-200ml/hr
- Pediatrics: 200 mL/hr

Urinary alkalinization:
- Target pH ≥ 7
- Minimum of 40 mEq/L sodium bicarbonate
- Po or IV

Therapeutic drug monitoring:
- Serum MTX levels
- Target clearance: 0.1-0.5 umol/L

Leucovorin calcium rescue:
- Competes with MTX for DHFR binding and repletes reduced folate stores
- Start 6 to 48hours after start of MTX
- If given too early → impact efficacy
- If given late (>48h) → increase toxicity
- Racemic mixture in Canada; available as I-leucovorin in USA (Levoleucovorin)

Management of toxic levels:

- Increase leucovorin as per nomogram; Refer to Lexicomp for additional guidance.
- Optimize IV fluids, urinary alkalinization and monitor urine output.
- Extracorporeal removal (high flux dialysis) has variable results; rebound serum levels up to 220%; always continue IV leucovorin.
- Glucarpidase (recombinant bacterial carboxypeptidase G2): 50Units/kg IV over 5 min; cleaves MTX into two non-toxic metabolites, resulting in ~97% reduction in plasma concentrations in 15 minutes. No effect on intracellular MTX, must continue leucovorin (separate by at least 2 hrs). Available only via SAP ($$$).