Antimetabolites

- **Folate antagonists:** methotrexate, pemetrexed, pralatrexate
- **Purine antagonists:** 6-mercaptopurine
- **Pyrimidine antagonists:** 5-fluorouracil, capecitabine, cytarabine, gemcitabine

Target the S phase of interphase of the cell cycle: DNA replication

**ANTI-FOLATES**

**Methotrexate**

High dose methotrexate (≥500 mg/m²) + leucovorin rescue

- High dose MTX → enters tumor cells via passive diffusion
- High dose MTX → ↑toxicity → requires leucovorin rescue

**Leucovorin rescue**

- Leucovorin is a reduced form of folic acid
- Purpose: replenishes supply of folate metabolites depleted by MTX → allows recovery of DNA synthesis in **normal** cells → ↓toxicity (e.g. myelosuppression, mucositis)
- Dosing: 15 mg/m², given 12hrs after HDMTX infusion, titrated based on MTX serum concentration
- Routes: PO, IM, IV (preferred)
- Goal serum MTX level: <0.1 μM

Preventing renal tubular necrosis

- **Hydration**
  - NS @ 100-125 mL/hr
  - Time frame: 6-12hr prior → 24hrs after MTX
  - Monitoring: urine output

- **Alkalization**
  - Rationale: MTX poorly soluble in acidic urine → precipitates in renal tubules → tubular injury → ↓pH → ↑precipitation
  - Goal: maintain urine pH >7.0
  - NaHCO₃ 50mEq/L of IV hydration – or – NaHCO₃ 100mg/m² po q6hr
  - Time frame: 6-12hr prior until 24hrs after MTX dose completion

**Routes of administration**

- IV: short or continuous infusion
- PO: weekly dose
- Intrathecal: 15mg flat dose, preservative free
- Ommaya reservoir: 6mg flat dose, preservative free
  - Surgically placed plastic reservoir in subgaleal space connected to lateral ventricle or tumor cyst by tubing

**Toxicities**

- Significant toxicities
  - Myelosuppression: dose-limiting
    - Neutropenia, thrombocytopenia, anemia
  - Hepatotoxicity
    - Chronic low doses → liver fibrosis
    - High dose MTX → acute LFT elevations that resolves in 7-14 days
  - GI toxicity: dose-limiting
    - Seen if ≥250mg/m²
    - Presentation: moderate emetogenic potential, mucositis if prolonged elevated MTX levels

- Risk factors: ↓CrCl, poor hydration, ↓urine output, acidic urine, pleural effusions, ascites

- Treatment for MTX toxicity: glucarpidase (Voraxaze)
  - Recombinant bacterial enzyme carboxypeptidase
  - MOA: hydrolyzes folic acid & antifolates
  - Indication: patients with impaired renal function (not normal pts) that leads to delayed MTX clearance (>0.1 μM)
  - Dose: 50 U/kg iv over 5 mins
  - Drug interactions with leucovorin (a glucarpidase substrate): do not give within 2 hrs of glucarpidase dose
  - Precautions
    - Anaphylaxis

\[
BSA = \sqrt{\frac{Ht (cm) \times Wt (kg)}{3600}}
\]
- MTX levels unreliable if within 48hrs of glucarpidase dose
- Continue leucovorin until goal MTX level maintained for 3 days → base leucovorin dose on patient’s pre-glucarpidase MTX concentration, give 48hrs after glucarpidase admin
- Continue hydration + alkalinization

**Dosing adjustments:** both renal & hepatic considerations

<table>
<thead>
<tr>
<th>Renal dosing adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl</td>
</tr>
<tr>
<td>&gt; 80 mL/min</td>
</tr>
<tr>
<td>80 mL/min</td>
</tr>
<tr>
<td>60 mL/min</td>
</tr>
<tr>
<td>50 mL/min</td>
</tr>
<tr>
<td>&lt; 50 mL/min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatic dosing adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bili</td>
</tr>
<tr>
<td>2-3 x ULN</td>
</tr>
<tr>
<td>&gt; 3 x ULN</td>
</tr>
</tbody>
</table>

- Drug interactions:
  - Renal: avoid nephrotoxic drugs, drugs competing for renal excretion (NSAIDs, probenecid, PCN), and PPIs (delays clearance)
  - Protein displacement: salicylates & sulfonamides → displace MTX from binding sites → ↑MTX toxicity

**Pemetrexed** *(Alimta)*

- **Dose:** 500 mg/m² IVPB over 10 min (good for admin on outpatient basis)
  - Dosing adjustments: renal only → do not admin with CrCl <45 mL/min
- **Toxicities**
  - Myelosuppression: dose-limiting, pretreat with Vit B₁₂ 1000mcg IM q3 cycles + folic acid 1mg po qd for 21 days post last dose
  - Rash: pretreat with dexamethasone 4mg po bid x 3 days starting prior to chemo
  - GI toxicity: mild emetogenic potential, mucositis, diarrhea
- **Drug interactions:** NSAIDs
  - CrCl 45-79 mL/min: use NSAIDs with caution
  - Short t½ NSAIDs (e.g. diclofenac, indomethacin): avoid 2 days prior until 1 day after pemetrexed
  - Long t½ NSAIDs (e.g. meloxicam, nabumetone): avoid 5 days prior until 2 days after pemetrexed

**Pralatrexate** *(Folotyn)*

- **MOA:** competitively (−)dihydrofolate reductase + (−)fotylpolyglutamyl synthase → depletion of thymidine
- **Dose cycle:** 30 mg/m² IVP over 3-5mins qweekly x 6 weeks + 1 week of rest
  - Dose adjustments: none studied for renal/hepatic, but need to adjust for mucositis and hematological toxicities
- **Toxicities:** myelosuppression, low emetogenic potential, mucositis, TEN (black box), tumor lysis
- **Premedications:** folic acid + cyanocobalamin (vit B₁₂)
  - Folic acid 1-1.25mg qd starting 10 days prior until 30 days after last pralatrexate dose
  - Cyanocobalamin (vit B₁₂) 1mg IM starting ≤10 weeks prior to first pralatrexate dose, q8-10 weeks
- **Drug interactions** may delay pralatrexate renal clearance: probenecid, NSAIDs, Bactrim

**PURINE ANTAGONISTS**

**6-Mercaptopurine**

- **Dose:** available as 50mg tablets po only → give on empty stomach
  - Dose adjustments: needed for myelosuppression, hepatic & renal impairment, TPMT enzyme deficiencies, concurrent allopurinol
- **Toxicities:** myelosuppression (dose-limiting), hepatic (intrahepatic cholestasis, liver failure), GI (low emetogenic potential, mucositis)
**PYRIMIDINE ANTAGONISTS**

**5-Fluorouracil**
- **Dose:** 200-1000 mg/m² IV (bolus or continuous infusion)
  - Radiosensitizer: need to ↓ dose
- **Leucovorin:** enhances 5-FU efficacy
  - MOA: ↑ binding affinity of 5-FU to thymidylate synthetase → ↑ cytotoxic activity
  - Give prior to 5-FU bolus
  - Levo-leucovorin given as 50% of dose due to drug shortage
- **Toxicities**
  - Dose limiting toxicities based on administration:
    - Bolus: myelosuppression, mucositis, and diarrhea
    - Continuous infusion: hand foot syndrome + same as bolus (though less so)
  - Cardiac: angina, myocardial ischemia
  - Skin: discoloration, nail changes
  - DPD deficiency: deficiency in rate limiting enzyme of 5-FU catabolism results in severe toxicity

**Capecitabine** (Xeloda)
- **Dose:** 1250 mg/m²/dose q12hr x 14 days repeated q21 days
  - Not well tolerated → most patients never reach this goal
  - Dose adjustments:
    - Renal: 30-50 mL/min @ 75% dose; <30 mL/min contraindicated
    - Hepatic: mild/moderate @ full dose + monitoring; if severe then abnormalities may reflect liver metastases
    - Radiosensitizer: 800-825 mg/m² po bid
- **Toxicities:** hand foot syndrome (dose limiting), GI (dose limiting diarrhea, low emetogenic potential), liver (hyperbilirubinemia), myelosuppression, alopecia, mucositis
- **Drug interactions:** warfarin (↑ anticoag effect, black box, use LMWH instead), phenytoin (↑ levels)

**Cytarabine** (Ara-C)
- **Dose:** >1500 mg/m²
  - High dose → profound toxicities & cytarabine syndrome
    - Profound toxicities: CNS, conjunctivitis, rash
    - Cytarabine syndrome: fevers, myalgia, arthralgia, bone pain, rash
  - Dosing adjustments: renal only
- **Routes:** IV, SC, IT
- **Premedications:** antiemetics (prior to IV or SC), dexamethasone eye drops
- **Toxicities:** myelosuppression (dose-limiting), GI (moderate emetogenic potential, diarrhea, mucositis)

**Gemcitabine** (Gemzar)
- **Well-tolerated** overall
- **Toxicities:** myelosuppression (dose limiting), flu-like symptoms, mild emetogenic potential

<table>
<thead>
<tr>
<th>DLT</th>
<th>Other toxicities</th>
<th>Dose adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Myelosuppression, mucositis</td>
<td>Moderate emetogenicity, hepatotoxicity</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>Myelosuppression</td>
<td>Rash, mild emetogenicity, diarrhea, mucositis</td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>Myelosuppression, low emetogenicity, mucositis, TEN, tumor lysis</td>
<td>Mucositis &amp; myelosuppression</td>
</tr>
<tr>
<td>6-MP</td>
<td>Myelosuppression</td>
<td>Intrahepatic cholestasis, liver failure, low emetogenicity, mucositis</td>
</tr>
<tr>
<td>5-FU</td>
<td>Bolus: myelosuppression, mucositis, diarrhea</td>
<td>Angina, myocardial ischemia, discoloration, nail changes</td>
</tr>
<tr>
<td></td>
<td>Infusion: hand foot syndrome</td>
<td>DPD deficiency</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Hand foot syndrome, diarrhea</td>
<td>Low emetogenicity, hyperbilirubinemia, myelosuppression, alopecia, mucositis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal, radiosensitizers</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Myelosuppression</td>
<td>CNS, conjunctivitis, rash, cytarabine syndrome, moderate emetogenicity, diarrhea, mucositis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Myelosuppression</td>
<td>Mild emetogenic potential, flu-like symptoms, but well-tolerated</td>
</tr>
</tbody>
</table>