Alkylation Agents

- **Platinum derivatives**: cisplatin, carboplatin, oxaliplatin
- **Nitrogen mustards**: ifosfamide, cyclophosphamide
- **Triazenes**: temozolomide

**Overview**

- **Alkylation**: removal of alkyl group + substitution with H atom
- **MOA**: alkylation $\rightarrow$ pos charged ethylene immonium ion formation (-N-CH$_2$-CH$_2$)$^+$ $\rightarrow$ binds to e- rich nucleosites on DNA
  - Cytotoxic effects: misreading of DNA, mispairing of DNA, inhibition of DNA replication or transcription, single/double strand breakage in DNA
  - Sites more vulnerable: guanine’s N$_7$; adenine’s N$_1$, N$_3$, N$_7$; and cytosine’s N$_3$
- **Pharmacophores**: either monofunctional or bifunctional, which may alkylate different nucleotide bases
  - Bifunctional agents: bind adjacent nucleotide bases $\rightarrow$ intrastrand cross-links between two DNA strands
  - $\uparrow$Crosslinks $\rightarrow$ $\uparrow$cytotoxic activity
- Non-cell cycle phase specific
- **Toxicities** across the class: myelosuppression (DLT, except cisplatin), N/V, alopecia, secondary leukemias
- **Resistance**: due to cellular repair, reactions with cellular thiol components, $\downarrow$ drug uptake by tumor cells
- **Seven subsets of alkylation agents**: platinum derivatives, nitrogen mustards, triazenes, ethylenimines, nitrosoureas, alkyl sulfonates, procarbazine
  - Platinum derivatives: cisplatin, carboplatin, oxaliplatin
  - Nitrogen mustards: ifosfamide, cyclophosphamide
  - Triazenes: temozolomide

## Platinum Derivatives

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin</th>
<th>Carboptatin</th>
<th>Oxaliplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Testicular, ovarian, bladder &amp; neck, esophageal, &amp; lung cancers, sarcomas</td>
<td>Ovarian, lung, head &amp; neck, breast, cervical, and testicular cancers</td>
<td>GI cancers: colorectal, pancreatic, gastric</td>
</tr>
<tr>
<td><strong>Reconstitution</strong></td>
<td>500-1000ml NaCl</td>
<td>100ml NaCl</td>
<td>500ml D$_5$W</td>
</tr>
<tr>
<td><strong>Admin time</strong></td>
<td>2-3hrs</td>
<td>30-60mins</td>
<td>2hrs</td>
</tr>
<tr>
<td><strong>DLTs</strong></td>
<td>Nephrotoxicity, neurotoxicity</td>
<td>Myelosuppression</td>
<td>Neuropathy, myelosuppression</td>
</tr>
<tr>
<td><strong>Toxicities</strong></td>
<td>Ototoxicity, electrolyte disturbances (Mg, K, Phos), N/V (acute/delayed), high/mod emetogenicity</td>
<td>Hypersensitivity reactions, N/V (acute/delayed), moderate emetogenicity</td>
<td></td>
</tr>
<tr>
<td><strong>Monitoring parameters</strong></td>
<td>Scr &lt;1.5, UOP &gt;200ml/2hr, CBC + differentials, Mg, K, phos</td>
<td>Scr, CBC + differentials, Mg, K, phos</td>
<td>CBC + differentials</td>
</tr>
</tbody>
</table>

### Platinum hypersensitivity

- Type I IgE mediated hypersensitivity
- Black box warnings: carboplatin (with $\uparrow$cycles), oxaliplatin
- Mild/moderate symptoms: facial flushing, pruritus, edema, diaphoresis, erythematous rash
- Severe symptoms: hives, anaphylaxis, bronchospasm, tachycardia, respiratory arrest, hypo/hypertension
- Management: stop infusion $\rightarrow$ steroids, antihistamines $\rightarrow$ check BP & HR

### Cisplatin (Platinol)

- **MOA**: covalently binds DNA $\rightarrow$ (--)DNA polymerase & (--)DNA-dependent RNA polymerase
  - Inactive form has 2 Cl atom $\rightarrow$ in the active form, 2 Cl atoms displaced by H$_2$O
  - Stays in inactive form until it reaches tumor cells
  - Blood has high Cl concentrations to keep cisplatin in inactive form
  - When administering, need to use NaCl as vehicle to replace displaced Cl atoms
  - Activated complex interacts with intracellular nucleophilic sites on DNA, RNA, or protein $\rightarrow$ forms intrastrand cross-links
- **Nephrotoxicity**: dose-limiting toxicity
  - Two mechanisms: tubular dysfunction + $\downarrow$GFR $\rightarrow$ acute renal failure
• Tubular dysfunction: in straight section of proximal tubules
  • ↑Urinary excretion of enzymes, protein, & Mg
  • ↓Absorption of H₂O & Na in tubules
  • ↓GFR by up to 25%
  • Partially reversible, persistent
  • Monitor with 24hr urine collection
• Neurotoxicity: dose-limiting toxicity
  • Clinical presentation: ototoxicity, neuropathy (motor & sensory)
  • Results from cumulative repeated doses
• Electrolyte disturbances: Mg, K, phos
  • Admin IV Mg sulfate 2-4g upfront even if levels are normal
  • Replace K and phos prn
• High/moderate emetogenic potential
• Ototoxicity: irreversible damage to hair cells → high frequency hair loss & tinnitus
  • ↑Risk if TPMT gene variants

**Carboplatin** (Paraplatin)
• Analogue of cisplatin: a carboxycyclobutane moiety replaces Cl ions
  • Similar MOA as cisplatin → cross-links formed later
  • Cannot substitute carboplatin for cisplatin unless it has been studied in that tumor type already
• Nephrotoxicity: less than cisplatin
  • Still able to use in renally impaired patients → needs dose adjustment based on the Calvert equation
  • Calvert equation: based on target AUC (range: 6-8) and GFR
    \[ \text{Dose (mg)} = \text{Target AUC (mg/ml/min)} \times \left[ \text{GFR (ml/min)} + 25 \right] \]

**Oxaliplatin** (Eloxatin)
• MOA: converted into platinum analogue
• SAR: cyclohexane ring attached to nitrogen atoms
• Indication: GI malignancies
• Reconstitution: D₅W only
• Neuropathy: DLT
  • Acute: can’t tolerate cold
    • Onset minutes to hours after infusion start; duration up to 72hrs
    • Symptoms: paresthesia, hypothesia, dysthesia at extremities and around mouth
  • Delayed: presents like diabetic neuropathy
    • Due to cumulative dosing: after 6-8 cycles
    • Symptoms: sensory & motor changes
    • Prevention: IV Ca and IV Mg pre/post oxaliplatin, stop & go strategy
    • Management: dose reduction or d/c, tramadol, TCAs, gabapentin, SNRIs

**Nitrogen mustards**
• Agents: cyclophosphamide & ifosfamide
• MOA: metabolic activation (prodrugs) → formation of mustards → cross-link DNA strands → prevent cell division
• Toxicities
  • **Hemorrhagic cystitis** (bladder toxicity)
    • Cause: excretion of active metabolite acrolein into urinary bladder
    • Ifosfamide > cyclophosphamide
    • Tissue edema & ulceration → mucosal cells slough + smooth muscle necrosis → focal hemorrhage
    • Painful urination, ↑frequency, hematuria
    • Risk factors: IV admin, young age, ↑doses
    • Prevent: hydration + mesna (IV or PO)
      • Hydration: flushes acrolein out of bladder, ↓time for tissue damage
      • **Mesna**: uroprotective, always given before ifosfamide and high dose cyclophosphamide
        • MOA: liberates free thiol groups in bladder → neutralizes acrolein
Neurotoxicity

- **Cause:** penetrates BBB easily
- **Ifosfamide > cyclophosphamide**
- **Onset:** hours to days post treatment
- **Presentation:** encephalopathy (ataxia, confusion, hallucinations, coma)
- **Risk factors:** albumin <3.4 g/dL, ↑Scr, hypnatremia, bulky abdominal/pelvic disease, ↓performance status
- **Treatment:** dosage fractionation, continuous infusion, time

Myelosuppression: DLT, dose dependent, neutropenia & thrombocytopenia

N/V: acute or delayed

Nephrotoxicity: Fanconi syndrome (irreversible impairment of proximal tubules) → polyuria, metabolic acidosis, renal phosphate wasting

SIADH: with high IV doses

Alopecia

### Drug interactions

- ↑Toxicity: allopurinol, chloramphenicol, aprepitant (ifosfamide)
- ↓Efficacy: CYP2D6 and CYP3A4 inducers
- ↑Anticoag effects: warfarin

<table>
<thead>
<tr>
<th>Activation</th>
<th>Cyclophosphamide</th>
<th>Ifosfamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP450</td>
<td>CYP3A4, CYP2C9, CYP2D6</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Hemorrhagic cystitis</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Emetogenicity</td>
<td>Moderate/high</td>
<td>High</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>SIADH</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Route</td>
<td>PO/IV</td>
<td>IV</td>
</tr>
</tbody>
</table>

### Triazines

**Temozolomide** *(Temodar)*

- **Indications:** brain tumors (glioblastoma multiforme, anaplastic astrocytoma) → crosses BBB easily
  - GBM dose: initially low dose + radiation → then ↑dose x 5 days for maintenance
- **Formulations**
  - PO: admin on empty stomach at bedtime
  - IV: refrigerate, infuse in 250ml IV bag over 90 mins
- **Emetogenic potential**
  - PO: moderate/high (if >75 mg/m²) or minimal/low (if ≤75 mg/m²)
  - IV: moderate
- **Toxicities**
  - Myelosuppression: DLT
  - PCP: need prevention
  - Aplastic anemia: rare