**Topoisomerase Inhibitors**

**Topoisomerase**: isomerase enzymes that act on the topology of DNA

- Enzymes that regulate unwinding/overwinding of DNA strands in its double helix structure
- **Topo I**: cuts one strand of DNA
- **Topo II**: cuts both strands of DNA

**ONE >> Topoisomerase I inhibitors**

<table>
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<tr>
<th></th>
<th>Topotecan (Hycamtin)</th>
<th>Irinotecan (Camptosar)</th>
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<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Ovarian cancer, small cell lung cancer, cervical cancer</td>
<td>Metastatic colorectal cancers</td>
</tr>
<tr>
<td><strong>Dosage forms</strong></td>
<td>IV, PO</td>
<td>IV</td>
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<tr>
<td><strong>Dose adjustments</strong></td>
<td>Renal + hepatic, hematologic (neutropenia, thrombocytopenia)</td>
<td>Renal + hepatic, hematologic (neutropenia, thrombocytopenia, anemia), diarrhea, phenytoin</td>
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<tr>
<td><strong>DLTs</strong></td>
<td>Myelosuppression</td>
<td>Myelosuppression, diarrhea</td>
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<tr>
<td><strong>Other toxicities</strong></td>
<td>Alopecia, moderate emetogenicity</td>
<td>Moderate emetogenicity</td>
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<tr>
<td><strong>Metabolism</strong></td>
<td></td>
<td>CYP3A4 (e.g. phenytoin)</td>
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**Irinotecan toxicity**: dose limiting diarrhea

- **Early diarrhea**: within 24hrs
  - Cholinergic presentation
  - Treatment: atropine IV - or - Lomotil (atropine/diphenoxylate)
- **Delayed diarrhea**: >2 days later
  - Secretory presentation: more common
  - Treatment: loperamide or octreotide (if severe)

**Irinotecan metabolism**

- **CYP3A4 substrate** → drug interaction with phenytoin (CYP3A4 inducer) → need to switch to levetiracetam
- **Active metabolite**: SN-38
  - Irinotecan = prodrug
  - ↑Potency: 1000x > than parent compound
  - Conversion in liver
- **UGT1A1 metabolism**
  - SN-38 conjugated by UGT1A1 enzyme for excretion
  - Polymorphism of UGT1A1 → ↓ enzyme activity → accumulation of SN-38 → ↑ myelosuppression + ↑ diarrhea
    - Suspect if unexpected neutropenia 2x normal
    - 10% of Caucasian North American population
    - Diagnostic test: invader UGT1A1 molecular assay available
**Topoisomerase II inhibitors**

### Anthracyclines

<table>
<thead>
<tr>
<th>Doxorubicin</th>
<th>Daunorubicin</th>
<th>Epirubicin</th>
<th>Idarubicin</th>
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<tr>
<td>Solid tumors, leukemias, lymphomas</td>
<td>Solid tumors, leukemias, lymphomas</td>
<td>Breast cancer</td>
<td>Acute myeloid leukemia</td>
</tr>
</tbody>
</table>

- Anthracyclines are similar across the board
- **Dose related effects & toxicities**
  - Antitumor & myelosuppression: proportional to AUC
  - Cardiotoxicity: associated with peak levels
  - Prolonged infusions: ↓N/V, ↓cardiotoxicity, ↑mucositis
- **Dose adjustments:** hepatic impairment → based on total bilirubin
- **Adverse effects:** myelosuppression (DLT), mucositis, cardiotoxicity, alopecia, red urine & sweat discoloration, extravasation, moderate emetogenic potential
  - **Cardiotoxicity**
    - Mechanism: free radical intermediates → irreversible oxidative damage to cardiac tissue
    - Risk factors: high cumulative doses, age (elderly/very young), cardiac disease history, mediastinal radiation therapy, high dose infusion, concurrent trastuzumab use
    - Acute presentation: arrhythmias, pericarditis-myocarditis syndrome
    - Delayed presentation: ↓LVEF before CHF onset
    - Monitoring: MUGA or EKG at baseline and periodically
  - **Extravasation**
    - Vesicants: always give centrally
    - Management: dextrazoxane
      - Ice pack → remove 15mins prior to dextrazoxane admin
      - Dextrazoxane: 3 day regimen, infusion given within 6hrs
- **Liposomal anthracyclines:** liposomal anthracyclines, pegylated liposomal doxorubicin
  - Changes tissue distribution + slower release → ↓exposure to heart/muscle + avoid high peaks
  - Toxicities: hand foot syndrome, radiation recall reaction, fatigue, fever, anorexia, N/V, stomatitis, diarrhea, constipation, rash, myelosuppression
  - Dose adjustments: hand foot syndrome, hematologic toxicities, stomatitis, hepatic dysfunction

### Mitoxantrone

- Indications: lymphomas, prostate cancer
- DLT: myelosuppression
- Adverse reactions: low emetic potential, cardiotoxicity, blue-green discoloration of urine/sweat
  - No free radical formation → ↓cardiotoxicity

### Etoposide (Vepesid)

- Indications: testicular cancer, lung cancer
- **Dosage forms:** IV (<0.4 mg/mL avoid precipitation), PO (poor bioavailability, refrigerate)
- DLT: myelosuppression
- Adverse effects: moderate emetogenic potential, irritant, reversible alopecia, anaphylaxis
  - Not water soluble → dissolved in propylene glycol → if too quick of an infusion → alcohol syndrome
- Prodrug available: etoposide phosphate → water soluble, give if severe anaphylaxis to etoposide
Immunomodulators

**Thalidomide** (Thalomid)

- **Multiple MOAs**
  - **Immunomodulatory**: suppresses TNF-α production → down-regulation of cell surface adhesion molecules
  - **Anti-inflammatory**: suppresses macrophage involvement, modulates IL production, ↑ NK cells
  - **Anti-angiogenic**: (–)VEGF + (–)basic fibroblast growth factors
- **Indications**: erythema nodosum leprosum, multiple myeloma (in combo with dexamethasone)
- **Admin**: with glass of water, ≥1hr after evening meal, qHS
- **Adverse reactions**
  - **Common**: sedation (admin at bedtime), peripheral neuropathy, constipation
  - **Black box**: VTE (if in combo with dexamethasone; prophylax ASA, warfarin, or LMWH)
  - **Severely teratogenic** → need to go through STEPS program

**Lenalidomide** (Revlimid)

- 100x more potent than thalidomide
- **Indications**: multiple myeloma (in combo with dexamethasone), myelodysplastic sydnromes
- **Dosing adjustments**: renal, hematological
- **Admin**: with glass of water, ≥1hr after evening meal, at bedtime
- **Adverse reactions**
  - **Common**: myelosuppression, constipation, diarrhea, nausea, fatigue, dizziness, arthralgia, tremor
  - **Black box**: hematological toxicity, DVT, PE
  - **Other**: tumor flare, tumor lysis syndrome, angioedema, SJS, TEN
  - **Teratogenic** → need to go through RevAssist program