Microtubule Inhibitors: Vinca Alkaloids, Taxanes, and Epothilones

Objectives

- Discuss the characteristics of the vinca alkaloids, taxanes, and epothilones including:
  - Role in treatment
  - Mechanism of action
  - Side effects
  - Dosing and administration
- Identify drug specific traits of the various drugs in the class

Self-assessment

- What is the general mechanism of action common to vinca alkaloids, taxanes and epothilones?
  a) Topoisomerase inhibition
  b) Nucleotide analog
  c) Microtubule interference
  d) DNA alkylation

Self-assessment

- True or False:
  - Paclitaxel and ixabepilone require premedication for hypersensitivity reactions
  - Vinca alkaloids, taxanes, and epothilones are highly emetogenic

Self-Assessment

56 year old female with metastatic breast cancer, BSA = 2.5m². After failing AC-T, her MD prescribes ixabepilone 40mg/m². What is the correct dose:
- 100mg
- 88mg
- 80mg
- Ixabepilone only indicated for first line therapy.

Chemotherapy Sites of Action
**Cell Cycle**

- Cell division
- Transport
- Cell structure

**Microtubule Structure and Function**

- Microtubule function:
  - Cell division
  - Transport
  - Cell structure

**Neuropathy**

- Sensory: Tingling, Burning, Numbness
- Autonomic: Abdominal cramping, Constipation, Severe ileus, Urinary retention, Vocal cord dysfunction
- Motor: Muscle weakness, Deep tendon reflexes

**Vinca Alkaloids**

- Vincristine (Oncovin®)
- Vinblastine (Velban®, Velsar®)
- Vinorelbine (Navelbine®)

**Class Specific Considerations**

*Vinca alkaloids are vesicants*

- If extravasation occurs:
  - Stop injection immediately
  - Withdraw any remaining drug from the line
  - Apply warm compress
  - Prevention:
    - Give 2cc drug, check for blood return
    - Flush with at least 50cc fluid after administration

*Never administer intrathecally - FATAL*

**History**

- **Vinca alkaloids:** extract from the leaves of the periwinkle plant *Catharanthus roseus* (formerly *Vinca rosea*):
  - Vincristine (1963), vinblastine (1965), vinorelbine (1994)
- **Taxanes:** extract from the bark of the Pacific yew, *Taxus brevifolia*:
- **Epothilones:** isolated from the myxobacterium *Sorangium cellulosum*:
  - Ixabepilone (2007)
Vinca Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Net Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 3A4</td>
<td>Inducers ↓ effect, Inhibitors ↑ effect</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>↑ pulmonary toxicity</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>↑ hematological toxicity (vinorelbine only)</td>
</tr>
<tr>
<td>Macrolide antibiotics</td>
<td>↑ vinca concentrations</td>
</tr>
</tbody>
</table>

Vinca Alkaloid Pharmacokinetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>First phase half-life</th>
<th>Protein Binding</th>
<th>Metabolism</th>
<th>Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>7.6 minutes</td>
<td>48%</td>
<td>Hepatic</td>
<td>Biliary, some renal</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>3.7 minutes</td>
<td>99%</td>
<td>Hepatic</td>
<td>Biliary, some renal</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>2 to 8 minutes</td>
<td>80%</td>
<td>Hepatic</td>
<td>Biliary</td>
</tr>
</tbody>
</table>

Vincristine (Oncovin)

Vincristine (Oncovin) Indications

**FDA Approved**
- Acute Leukemia
- Non-Hodgkin’s Lymphoma
- Hodgkin’s Disease
- Neuroblastoma
- Wilm’s Tumor
- Rhabdomyosarcoma

**Off Label**
- Kaposi’s Sarcoma
- CNS tumors
- Breast
- Lung
- Bladder
- Testicular
- CLL
- Ewing’s Sarcoma

Vincristine Administration/Dosage

- **Recommended max** = 2mg weekly
- **Adult**
  - 1.5mg/m² IV bolus once weekly
  - 0.4mg/m²/day CIVI x 4 days Q28D (EPOCH regimen)
- **Pediatric**
  - 1.5mg/m² once weekly (>10 kg)
  - 0.05mg/kg once weekly for small children (<10kg)
- L-asparaginase: administer 12-24 hours following vincristine
- **Dose adjustments**
  - Tbil>1.5 - ↓ dose 50%
  - Tbil>3.0 - ↓ dose 75%

Vincristine Adverse Events

**Contraindicated**: demyelinating form of Marie-Charcot Tooth Syndrome

**Dose-Limiting Toxicity**: Neurotoxicity

**Common ADRs**: constipation, alopecia, mild myelosuppression

**Rare**: SIADH
Vinblastine (Velban, Velspar)

Vinblastine Indications

**FDA approved**
- Hodgkin’s Disease
- Non-Hodgkin’s Lymphoma
- Testicular
- Kaposi’s Sarcoma
- Choriocarcinoma
- Breast

**Off Label**
- Bladder
- Ovarian
- Prostate
- Esophageal
- Renal Cell

Vinblastine Administration/Dosage

- **Most common**
  - 6mg/m² IV bolus over 1 minute QWK
- **Initial**
  - Adults
    - 3.7mg/m² QWK, ↑ 1.5mg/m² each week
  - Children
    - 2.5mg/m² QWK, ↑ 1.5mg/m² each week
- **Max dose**
  - Adult – 18.5mg/m²
  - Children – 12.5mg/m²
- **Dose adjustment**
  - Tbili>1.5 - ↓ dose 50%
  - Tbili>3.0 - ↓ dose 75%

Vinblastine Adverse Events

- **Contraindicated**: ANC < 1000
- **Dose-Limiting Toxicity**:
  - Granulocytopenia (nadir 5-10 days, recovery 7-14 days)
- **Common ADRs**: alopecia, constipation, hypertension, fatigue
- **Rare**: SIADH, depression, Reynaud’s

Vinorelbine (Navelbine)

Vinorelbine Indication

**FDA Approved**
- Non-Small Cell Lung

**Off-Label**
- Breast
- Ovarian
- Head and Neck
- Hodgkin’s
- Renal Cell
- Melanoma
- Small Cell Lung
**Vinorelbine Dosage/Administration**

- **25-30mg/m²** IV over 6-10 min weekly or every 4 weeks if combined with cisplatin
- Dilute to **0.5-3mg/ml**
- **Dose adjustment**
  - Tbil i > 2.1 - ↓ dose 50%
  - Tbil i > 3.0 - ↓ dose 75%
  - ANC < 1500, episodes of fever and/or sepsis

**Vinorelbine Adverse Effects**

**Contraindicated:** ANC < 1000

**Dose-Limiting Toxicity:** Granulocytopenia
(nadir 7-10 days, recovery 7-14 days)

**Common ADRs:** alopecia, constipation, fatigue

**Rare:** interstitial pneumonitis, ARDS

**Case**

- 25 y.o. male with Hodgkin’s Lymphoma (HL) is coming in for first time infusion of R-CHOP. What counseling points should be made regarding vinblastine?

**Taxanes**

- Paclitaxel (Taxol®)
- Docetaxel (Taxotere®)
- Paclitaxel Protein-Bound Particles (Abraxane®)

**Taxanes Pharmacokinetics**

<table>
<thead>
<tr>
<th>Drug</th>
<th>First phase half-life</th>
<th>Protein Binding</th>
<th>Metabolism</th>
<th>Elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>13.1 to 52.7 hours</td>
<td>89 to 98%</td>
<td>Hepatic (CYP2C8 &amp; 3A4)</td>
<td>Biliary, some renal</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>11.1 hours</td>
<td>94 to 97%</td>
<td>Hepatic (CYP3A4)</td>
<td>Fecal, some renal</td>
</tr>
<tr>
<td>Albumin-bound pacltaxel</td>
<td>14.6 to 27 hours</td>
<td>89 to 98%</td>
<td>Hepatic (CYP2C8 &amp; 3A4)</td>
<td>Fecal, some renal</td>
</tr>
</tbody>
</table>

**Taxane Drug Interactions**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platinum Analouges</strong></td>
<td>↑ myelosuppression, give taxane before platinum</td>
</tr>
<tr>
<td><strong>Anthracyclines</strong></td>
<td>↑ anthracycline levels and toxicity</td>
</tr>
<tr>
<td><strong>CYP 3A4</strong></td>
<td>Inducers ↓ effect</td>
</tr>
<tr>
<td></td>
<td>Inhibitors ↑ effect</td>
</tr>
<tr>
<td><strong>CYP 2C8 &amp; 2C9</strong></td>
<td>Inducers ↓ effect</td>
</tr>
<tr>
<td>(paclitaxel only)</td>
<td>Inhibitors ↑ effect</td>
</tr>
<tr>
<td><strong>St. John’s Wort</strong></td>
<td>Decreased taxane levels</td>
</tr>
</tbody>
</table>
Paclitaxel (Taxol)

Paclitaxel (Taxol) Adverse Effects

**Contraindicated:** ANC < 1500, hypersensitivity to Cremophor® EL

**Dose-Limiting Toxicity:** neutropenia (nadir 11 days, rapid recovery)

**Common ADRs:** peripheral neuropathy, myalgia/arthralgia, alopecia, mild hypersensitivity reactions, anemia

**Rare:** severe hypersensitivity reactions (<2%), cardiac conduction abnormalities

Paclitaxel Dosage/Administration

- **Intraperitoneal Paclitaxel**
  - Ovarian CA
    - 16 month survival benefit vs. IV paclitaxel
      - with cisplatin
    - ↑ hematologic, metabolic, and neurologic toxicity (compared to IV)
      - IP doses were higher than IV

Paclitaxel Indications

**FDA Approved**
- Breast
- Ovarian
- Non-small Cell Lung
- Kaposi's Sarcoma

**Off-Label**
- Cervical
- Head & Neck
- Prostate
- Unknown Primary
- Testicular

Paclitaxel Dosage/Administration

**Premeds:** Diphenhydramine 50mg IV, Famotidine 20mg IV, Dexamethasone 20mg IV 30 - 60 min prior to infusion

**Dosage**
- 135-250mg/m² IV over 3 - 24 hrs repeated every 3 weeks
- 60-100mg/m² IV over 1 hr for weekly dosing
- 40-60mg/m² IV over 1hr weekly with radiation treatment
- Dose adjustments necessary for hepatic dysfunction

**Administration**
- Concentration: 0.3-1.2 mg/ml
- Use non-PVC bags and lines with a 0.22 micron filter

Docetaxel (Taxotere)

Docetaxel (Taxotere) Adverse Effects

- Peripheral neuropathy, myalgia/arthralgia, hematologic, metabolic, and neurologic toxicity (compared to IV
- Non-small cell lung: rapid recovery

Paclitaxel Dosage/Administration

- 40-60mg/m² IV over 1hr weekly with radiation treatment
- 135-250mg/m² IV over 3 - 24 hrs repeated every 3 weeks
- Non-small Cell Lung
- Breast
- FDA Approved

Docetaxel (Taxotere) Indications

- 16 month survival benefit vs. IV paclitaxel
Docetaxel Indications

FDA Approved
• Breast
• Non-Small Cell Lung
• Squamous Cell Head & Neck
• Hormone Refractory Prostate
• Gastric Adenocarcinoma

Off Label
• Bladder
• Esophagus
• Ovarian
• Small Cell Lung

Docetaxel Adverse Effects

Contraindicated:
ANC < 1500, hypersensitivity to polysorbate 80, liver abnormalities (bilirubin > ULN, or AST/ALT > 1.5 ULN with alk phos > 2.5 ULN)

Dose-Limiting Toxicity:
bone marrow suppression
(neutropenia: nadir 7 days, median duration 7 days)

Common ADRs:
fluid retention, tearing, skin reactions/nail disorders, neuropathy, HSR, mucositis, myalgia/arthritis, asthenia, alopecia

Rare:
severe hypersensitivity reactions (2.2%), onycholysis (0.8%), cardiac conduction abnormalities, hepatitis

Docetaxel Dosage/Administration

Premedicate with dexamethasone 8mg PO BID x 3 days starting the day prior to therapy

Dosage
• 60 - 100mg/m2 IV over 1hr every 3 weeks
• 35mg/m2 IV over 1hr weekly
• Dose adjustments necessary for hepatic dysfunction

Administration
• Concentration: 0.3-0.74mg/ml
• Use non-PVC bags and lines with a 0.22 micron filter

Abraxane: Paclitaxel Albumin-Bound Particles

• Albumin-stabilized particle
• Improved paclitaxel solubility
• Less toxic than solvent formulation
• Albumin receptor-mediated paclitaxel transport mechanism
  -- facilitates the passage of paclitaxel through the bloodstream to the underlying tumor tissue

Abraxane Adverse Effects

Abraxane Indications

FDA Approved
• Breast cancer after failure of anthracycline regimen

Off Label
• Anal
• Head and Neck
• Non-small Cell Lung

Abraxane Adverse Effects

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Abraxane® 260mg/m2</th>
<th>Paclitaxel 175mg/m2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia All Grades</td>
<td>80%</td>
<td>82%</td>
</tr>
<tr>
<td>Neutropenia (ANC&lt;500)</td>
<td>9%</td>
<td>22%</td>
</tr>
<tr>
<td>Infections</td>
<td>24%</td>
<td>20%</td>
</tr>
<tr>
<td>Anemia (Hgb &lt; 11g/dL)</td>
<td>33%</td>
<td>25%</td>
</tr>
<tr>
<td>Sensory Neuropathy G 3</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>4%</td>
<td>12%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18%</td>
<td>10%</td>
</tr>
</tbody>
</table>
Abraxane Dosage/Administration

**Dosage**
- 260mg/m² IV over 30 minutes every 3 weeks
- 100mg/m² IV over 30 minutes weekly

**Administration**
- Final solution is a milky appearing
- Final concentration = 5mg/ml, does not require further dilution

No hypersensitivity premedication required

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Case

- 56 y.o. female is admitted for treatment of non-small cell lung cancer (NSCLC). She is to be treated with paclitaxel and carboplatin. Which pre-medications will she need before beginning her infusion?

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Epothilones

Ixabepilone (Ixempra®)

[Image](https://upload.wikimedia.org/wikipedia/commons/thumb/b/b7/Ixabepilone.svg/800px-Ixabepilone.svg.png)

Ixabepilone Pharmacokinetics

- Volume of Distribution
  - At least 1000L
- Metabolism
  - Hepatic inactivation (CYP3A4)
- Half-life
  - 52 hours
- Elimination
  - 21% renal, 65% feces

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Ixabepilone (Ixempra)

[Image](https://upload.wikimedia.org/wikipedia/commons/thumb/b/b7/Ixabepilone.svg/800px-Ixabepilone.svg.png)

Ixabepilone Indications

**FDA Approved**
- Advanced/metastatic breast cancer
  - In combination with capecitabine, in tumors resistant to other therapies
  - Alone in tumors resistant to other therapies including capecitabine

**Off Label**
- Hormone refractory, metastatic prostate cancer
Ixabepilone Adverse Effects

**Contraindicated:** ANC < 1500, hepatic impairment in combo with capecitabine (bilirubin > ULN or AST/ALT > 2.5 ULN), Cremophor EL hypersensitivity

**Dose-Limiting Toxicity:** bone marrow suppression

**Common ADRs:** peripheral neuropathy, motor neuropathy, fatigue, myalgia/arthritis, alopecia, mucositis, N/V, diarrhea, skin/nail disorders

**Rare:** severe hypersensitivity reactions (1%), tearing

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Ixabepilone Dosage/Administration

**Premeds:** Diphenhydramine 50mg IV, Famotidine 20mg IV, Dexamethasone 20mg IV 30 - 60 min prior to infusion

**Dosage**
- 40mg/m² IV over 3 hours every 3 weeks
- Max BSA = 2.2
- Dose adjustments necessary for hepatic dysfunction

**Administration**
- Concentration: 0.2-0.6mg/ml
- Use LR or buffered NS in non-PVC bags and lines with a 0.2-1.2 micron filter

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Self-assessment

- What is the general mechanism of action common to both vinca alkaloids and taxanes?
  a) Topoisomerase inhibition
  b) Nucleotide analog
  c) Microtubule interference
  d) DNA alkylation

**Self-assessment**

- True or False:
  - Paclitaxel and ixabepilone require premedication for hypersensitivity reactions
  - Vinca alkaloids, taxanes, and epothilones are highly emetogenic

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Self-Assessment

56 year old female with metastatic breast cancer, BSA = 2.5m². After failing AC-T, her MD prescribes ixabepilone 40mg/m². What is the correct dose:
- a) 100mg
- b) 88mg
- c) 80mg
- d) Ixabepilone only indicated for first line therapy.

**Questions?**
References