Overview of Vinca Alkaloids

Susannah Koontz, PharmD, BCOP
Clinical Specialist – Pediatric Oncology

The following material was presented to Adult and Pediatric Medical Oncology Fellowship Trainees at M. D. Anderson Cancer Center as part of their core curriculum series in 2006
Introduction & History

- Extracts of the periwinkle plant
  *(Catharanthus roseus – formerly known as Vinca rosea)*

The French referred to it as “violet of the sorcerers”

Early uses
- Scurvy
- Toothaches
- Controlling hemorrhage
- Diabetes – investigated as a hypoglycemic agent by Eli Lily
**Introduction & History**

- Anticancer activity first noted in 1957 in rats (Bone marrow suppression and antileukemic effects)
- Cytotoxicity activity occurs through the disruption of microtubules

**US commercially available agents**
- Vincristine (Oncovin®)
- Vinblastine (Velban®)
- Vinorelbine (Nalvelbine®)

**US investigational agents**
- Liposomal vincristine (Marqibo®)
- Vindesine (Eldisine®)
Structures and Chemistry

- Two linked components
  - Dihydroindole nucleus = Vindoline
  - Indole nucleus = Catharanthine
  - Linked by carbon-carbon bond
**Microtubules**

- Integral components of mitotic spindle
- Composed of tubulin with each heterodimer consisting of 2 subunits – α- and β-tubulin
  - Tubulin molecules assemble into microtubules by forming linear protofilaments
  - Microtubules are composed of 13 protofilaments aligned side-by-side around a hollow core with α- and β-tubulin subunits alternating with each other
**Microtubules**

- Microtubule is in dynamic equilibrium between assembly and disassembly
- Cellular functions
  - Neurotransmission
  - Mitosis
- Polymerized tubulin can be modified and can serve as binding sites for microtubule associated protein (MAP)
  - Stabilize microtubules against disassembly

**Mechanism of Action**

- Inhibition of microtubule assembly through tubulin interaction and disruption
- Specific for M phase
- Correlations have been made between cytotoxicity and dissolution of mitotic spindles
Mechanism of Action

- **Drug concentration and exposure**
  - Concentration that inhibits cell proliferation is directly related to concentration that induces metaphase arrest in 50% of cells
    - Low concentrations → stabilize microtubule length and leads to inhibition of mitosis
    - High concentrations → disruption of microtubules
  - **Duration of drug exposure above a specific threshold may be most important factor for cytotoxicity**

- **Other**
  - Disrupts structural integrity cells rich in tubulin as well as the cell membrane and functions
  - Induces morphological changes in cells during G1 and S phases
  - Competes for transport of amino acids into cells
  - Inhibits purine biosynthesis
  - Inhibits RNA, DNA and protein synthesis by blocking glutamic acid utilization
  - Inhibits angiogenesis
Drug Resistance

- Related to decrease drug accumulation and retention within cells
- Two main types of resistance
  - Multidrug resistance
  - Alterations in tubulin proteins

Drug Resistance

- Multidrug resistance (MDR)
  - Overexpression of mdr-1 gene
  - P-glycoprotein (Pgp) works as an energy dependent efflux pump
  - Drug resistance $\sim [\text{Pgp}]$
  - In vitro reversal of inhibition by calcium channel blockers, antihypertensives, antiarrhythmics, antibiotics, and cyclosporine
Drug Resistance

- Alterations in α- and β-tubulin proteins
  - Results in decreased drug binding or increase resistance to microtubule disassembly
  - Overexpression of β-III isotype of β-tubulin
  - Decreased binding affinity of tubulin for alkaloids

FDA-Approved Indications

- Vincristine
  - ALL (Hyper-CVAD)
  - NHL (CHOP)
  - Hodgkin’s Lymphoma (MOPP)
  - Neuroblastoma
  - Rhabdomyosarcoma
  - Wilms’ Tumor
FDA-Approved Indications

- Vinblastine
  - Testicular
  - Hodgkin’s Lymphoma (ABVD)
  - NHL
  - Breast
  - Choriocarcinoma
  - Malignant histiocytosis
  - Mycosis fungoides
  - Kaposi’s sarcoma

FDA-Approved Indications

- Vinorelbine
  - NSCLC
Examples of Uses

**NHL – CHOP**
- Cyclophosphamide 750 mg/m² IV D1
- Doxorubicin 25 mg/m² CIVI D1-2
- *Vincristine 1.4 mg/m² (max 2 mg) IV D1*
- Prednisone 100 mg/day PO D1-5
- Repeat every 21 days

Examples of Uses

**ALL - HyperCVAD**
- Cyclophosphamide 300 mg/m² q12H x 6 doses D1-3
- Mesna 600 mg/m²/day CIVI D1-3
- *Vincristine 2 mg IV days 4 and 11*
- Doxorubicin 50 mg/m² CIVI day 4
- Dexamethasone 40 mg IV or PO days 1-4 and 11-14
Examples of Uses

- Multiple Myeloma – VAD
  - **Vincristine 0.4 mg/day CIVI D1-4 (max 2 mg)**
  - Doxorubicin 9 mg/m2 CIVI over 24 hours D 1-4
  - Dexamethasone 20 mg/m2/day PO D1-4, 9-12, and 17-20
  - Repeat q 28 days

Examples of Uses

- Hodgkin’s disease – ABVD
  - Doxorubicin 25 mg/m2 IV D1,15
  - Bleomycin 10 units/m2 IV D1, 15
  - **Vinblastine 6 mg/m2 IV D1, 15**
  - Dacarbazine 375 mg/m2 IV D 1,15
Examples of Uses

- NSCLC
  - Vinorelbine 30 mg/m2 IV D 1, 8, 15

Pharmacokinetics

- Demonstrates a 3 compartment model
- High degree of drug binding in peripheral tissues
  - Large Vd
  - High Cl
  - Long terminal t1/2
- Vincristine has longest half-life and lowest rate of Cl
- Vinblastine has shortest half-life and highest rate of Cl
Pharmacokinetics

- **Absorption**
  - Given as IV infusions
  - Vinorelbine has an oral $F = 27\text{-}46\%$

Pharmacokinetics

- **Distribution**
  - Tiphasic
  - Poor CNS penetration
  - Extensive binding to proteins
    - 75\% for vincristine
    - 99\% for vinblastine
    - 80\text{-}90\% for vinorelbine
  - Vinorelbine has greatest distribution into tissues
  - Vincristine has greatest binding to RBC/Plts
Pharmacokinetics

- Metabolism
  - Liver
  - Mediated by P450 system, most commonly the CYP3A4 subfamily
  - Vincristine has 6-11 metabolites
  - Vinblastine → desacetylvinblastine (active)
  - Vinorelbine → deacetylvinorelbine (as active as parent compound) and vinorelbine N-oxide

Pharmacokinetics

- Excretion
  - Half-life
    - Vincristine: 23-85 hrs
    - Vinblastine: 20-64 hrs
    - Vinorelbine: 27.7-43.6 hrs
  - Biliary excretion
  - Fecal elimination (46-95%)
  - Little urinary excretion (< 20%)
Dosing & Dose Adjustments

- Vincristine
  - 0.4-1.4 mg/m² repeated weekly
  - “Capping of 2 mg”
    - Historically done b/c of neurotoxicity
    - Needs to be re-evaluated
  - No dose adjustments for renal impairment
  - Dose adjustments for hepatic impairment

Dosing and Dose Adjustments

- Vinblastine
  - 4-12 mg/m² Q 7-10 days
  - Dose adjustments are recommended based on WBC (causes leukopenia)
  - Dose adjustments required for hepatic impairment
Dosing and Dose Adjustments

- **Vinorelbine**
  - 30 mg/m2 Q week
  - Dose adjustments based on ANC
  - Dose adjustments based on hepatic impairment
  - May need to hold doses based on degree of neurotoxicity

Dosing and Dose Adjustments

- **Hepatic Impairment**

<table>
<thead>
<tr>
<th>T.bil</th>
<th>SGOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.5</td>
<td>&lt;60</td>
</tr>
<tr>
<td>1.5-3</td>
<td>60-180</td>
</tr>
<tr>
<td>3.1-5</td>
<td>&gt;180</td>
</tr>
<tr>
<td>&gt;5</td>
<td></td>
</tr>
</tbody>
</table>

- **Vincristine**
  - Give 100% of dose
  - Give 50% of dose
  - Give 25% of dose
  - Omit

- **Vinblastine**
  - Give 100% of dose
  - Give 50% of dose
  - Give 25% of dose
  - Omit

- **Vinorelbine**
  - Give 100% of dose if < 2 mg/dL
  - 2.1 - 3 mg/dL give 50% of dose
  - > 3 mg/dL give 25% of dose
  - Unknown
Adverse Effects – Hematological

- **Vincristine**
  - Mild leukopenia and thrombocytopenia
  - Onset 7 days, Nadir 10 days, Recovery 21 days

- **Vinblastine**
  - Dose limiting toxicity (DLT)
  - Dose dependent profound neutropenia; thrombocytopenia and anemia less common
  - Nadir 5-10 days, Recovery 7-21 days

- **Vinorelbine**
  - Neutropenia is DLT; anemia is common
  - Onset 7-10 days; Recovery 14-21 days

Adverse Reactions – Neurological

- **Vincristine**
  - Peripheral neuropathy is the DLT

- **Vinblastine**
  - Less common than with vincristine
  - Paresthesias, loss of deep tendon reflexes, peripheral neuritis, HA, mental depression, convulsions
  - Use in caution with other ototoxic agents

- **Vinorelbine**
  - Mild to moderate peripheral neuropathy
  - Prior therapy with paclitaxel may lead to cumulative neurotoxicity
Adverse Reactions – Neurological

- Binding of tubulin in nerves leads to blocking of axonal transport that causes the damage
- Usually starts as symmetrical sensory impairment and paresthesias in extremities ("stocking-glove" sensations)
- Motor dysfunction, foot and wrist drop and paralysis can occur

Adverse Reactions – Neurological

- Can persist for months after treatment has stopped and motor neurotoxicity may be irreversible
- Autonomic polyneuropathy
  - Cranial nerve palsies that lead to hoarseness, diplopia and facial palsies
- Depression, confusion, seizures and coma are more rare
Adverse Reactions – Neurological

- Risk factors
  - Age > 40 yrs old
  - Short interval between doses
  - Concurrent etoposide or XRT
  - Single doses greater than 2 mg
  - Cumulative dose (usually seen after 5-6 mg)
  - Underlying or pre-existing neuropathy or myopathy
  - Malnutrition
  - Obstructive liver disease

- May require dose and/or frequency reductions or interruptions
- Protective measures?
  - Thiamine, vitamin B12, pyridoxine and folic acid have been used with limited success
  - Glutamic acid
    - Competitive inhibition of carrier-mediated vincristine transport at cell membrane level and enhances microtubule stability
    - More studies are needed
Adverse Reactions – Neurological

- Protective measures (?) – continued
  - Amifostine
    - Protection of nerve tissue
  - Insulin growth factor (IGF) and nerve growth factor (NGF) are being studied

Adverse Reactions – GI

- Vincristine
  - Constipation very common requiring stool softeners +/- stimulant laxative
  - Paralytic ileus (more common in pediatrics)
  - Metallic taste in mouth
  - Emetogenicity level 1

- Vinblastine and vinorelbine
  - Constipation can occur
  - Stomatitis and pharyngitis more common than with vincristine
  - Emetogenicity level 1
Adverse Reactions – Dermatologic

- Alopecia
  - Common, not total body
  - Reversible without stopping therapy
- Rash
- Hand-foot syndrome with CIVI vinorelbine

Adverse Reactions – Endocrine

- SIADH can be seen with all agents and usually subsides within 2-3 days after onset
- Electrolyte abnormalities with vincristine
  - Hyperuricemia
  - Hypokalemia
  - Hyponatremia
Adverse Reactions – Hepatic

- Vincristine
  - VOD reported
- Vinblastine
  - Transient hepatitis
- Vinorelbine
  - Increases in SGPT and alkaline phosphatase

Adverse Reactions – Pulmonary

- Bronchospasm
  - Oxygen
  - Corticosteroids
  - Bronchodilators
- ARDS
- Pulmonary infiltrates are rare
Adverse Reactions – Other

- Jaw pain
- Retinal changes, optic atrophy and cortical blindness with vincristine
- Hypertension can be frequent with vinblastine
- Raynaud’s phenomenon
- Ototoxicity
- Radiation recall with vinorelbine

Drug Interactions

- Major CYP3A4 substrate
- CYP3A4 inducers can increase clearance of vincas
  - Phenytoin and carbamazepine
  - Phenytoin levels may be decreased by up to 50%
Drug Interactions

- CYP3A4 Inhibitors can inhibit the metabolism of vincas as well as inhibit the Pgp efflux pump
  - Azoles, erythromycin, aprepitant, ciprofloxacin
  - With the azoles, you may need to withhold the antifungal (consider another class of antifungals)

Drug Interactions

- Digoxin
  - Altered absorption of digoxin
- L-asparaginase
  - Decreases Cl of vincas
  - Give vinca 12-24 hours before L-asparaginase to decrease toxicity
- Methotrexate
  - Increased accumulation of methotrexate inside cells since vincas block drug efflux
Drug Interactions

- **Zidovudine (AZT)**
  - Vincas inhibit the metabolism of AZT to its active metabolite
  - Watch for hematological toxicity
- **Cisplatin**
  - Enhances vinorelbine’s granulocytopenia
- **Taxanes**
  - Increased neurotoxicity

Drug Interactions

- **Gefitinib**
  - Increased myelotoxicity with vinorelbine
  - Avoid combination
- **St. John’s Wort**
  - May decrease levels of vincristine
Administration Considerations

- Given as short infusions over several minutes (usually 15-30 minutes)
  - Agents are vesicants!
- May be given as CIVI (vincristine)
- May be given as IV push
  - MDACC has eliminated this method to decrease the chance of inadvertent intrathecal administration

Administration Considerations

- Vesicant
  - Stop infusion
  - Attempt aspiration of residual drug in tissue
  - Local heat for 1 hour QID x 3-5 days
  - Hyaluronidase 150 units SQ (25 gauge needle) via 6 clockwise injections circumferentially into surrounding tissue
  - Corticosteroids may be useful
  - Plastic surgery consult for possible debridement
Administration Considerations

- Intrathecal administration
  - Induces a severe myeloencephalopathy
    - Ascending motor and sensory neuropathies
    - Encephalopathy → Death
  - Numerous safe guards in place to prevent accidents

- Intrathecal administration procedures
  - Remove as much drug as possible through lumbar access
  - Epidural catheter into subarachnoid space via intravertebral space above the initial lumbar access site → irrigate with LR at 150 ml/hr
  - Neurosurgery → CSF exchange/lavage
  - May need FFP
Administration Considerations

- Intrathecal administration
- Supportive measures
  - Glutamic acid 10 gm CIVI over 24 hrs followed by 500 mg PO TID x 1 month
  - Folinic acid 100 mg IV bolus then 25 mg/hr x 24 hours then 25 mg IV Q 6 hours x 1 week
  - Pyridoxine 50 mg IV Q 8 hrs

Liposomal Vincristine

- Developed using a transmembrane carrier system
- Sphingosomal drug delivery that allows targeted therapy with decrease in toxicity
  - Small liposomes can selectively extravasate in tumor’s leaky vasculature
- Local drug delivery via slow release of drug at tumor site
  - 50% of drug released in 24 hours
  - 100% released in 72 hours
Liposomal Vincristine

- Longer circulating half-life
- Dose is 2 mg/m2 IV over 1 hour
- Similar ADR but less neurotoxicity
- More information can be found at www.inexpharm.com
References


References

