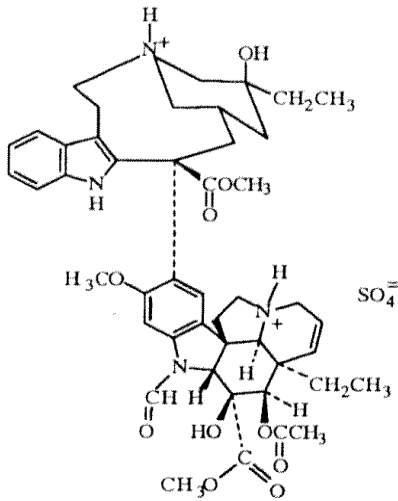


Lecture 11: Antimitotic agents –cell cycle specific (M phase mainly)

1. Vinca alkaloids (we will discuss 3)

Vincristine (Oncovin):



Uses: Acute leukemia, Hodgkin's lymphoma (part of the MOPP, COPP, BEACOPP regimens); non-Hodgkin's lymphoma (CHOP: cyclophosphamide/hydroxydaunorubicin/**oncovin**/prednisone); acute lymphocytic leukemia (ALL) if Ph-; neurosarcoma, Wilm's tumor (nephroblastoma). Administration by IV only; intrathecal administration can be fatal. Vinca alkaloids are light sensitive.

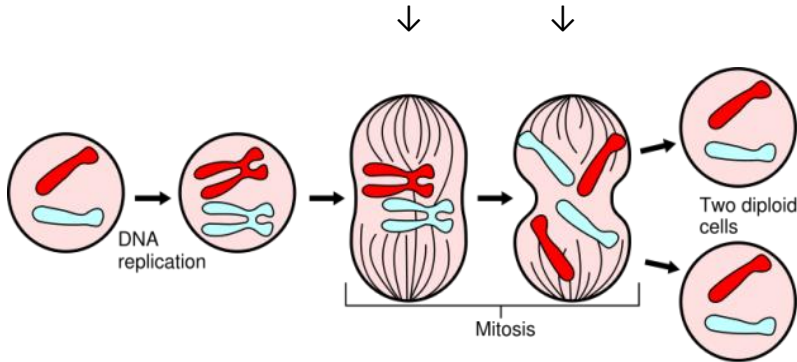
Mechanism: Binds to microtubules in the spindle apparatus and prevents their proper function (Figure 1). Specifically, it binds at interface of α and β tubulin heterodimers and inhibits tubulin polymerization. Opposite mechanism of taxanes (below) but the end result is similar.

Toxicity: Peripheral neuropathy*, constipation, paresthesia, alopecia; but myelosuppression occurs but not severe. Extravasation injury can occur. *Peripheral neuropathy can be severe and a reason to stop or avoid use of vincristine. A person with a family history of Charcot-Marie-Tooth disease (CMT) may benefit from genetic testing for CMT before taking vincristine because CMT causes a form of peripheral neuropathy.

ADME: Tri-phasic elimination with very long terminal t_{1/2} being ~100 hrs; clearance mainly hepatic with involvement of CYP3A4. Use of strong inhibitors of CYP3A4 can increase toxicity especially peripheral neuropathy.

Note(s): A natural product (di-alkaloid) initially isolated from the common Periwinkle plant.

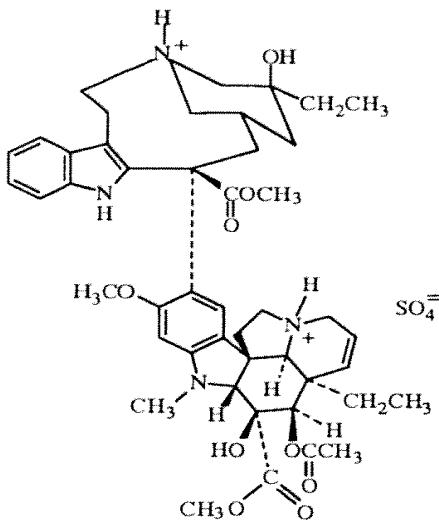
Figure 1. The cell cycle showing the role of the spindle apparatus in cell division (mitosis)



Vincristine sulfate (Marqibo): approved Aug 2012

Marqibo is a liposomal formulation (sphingomyelin/cholesterol) of vincristine. It is used in the relapse setting in adults with acute lymphocytic leukemia (ALL) that is Philadelphia chromosome negative (Ph⁻); liposome form also aids tissue penetration and reduces toxicities.

Vinblastine (Velbe):



Uses: Hodgkin’s lymphoma, non-small cell lung cancer, breast cancer. A component of **VBM** (**vinblastine**/bleomycin/methotrexate) or **ABVD** regimens for Hodgkin’s lymphoma. Administration by IV only; intrathecal administration can be fatal. Vinca alkaloids are light sensitive.

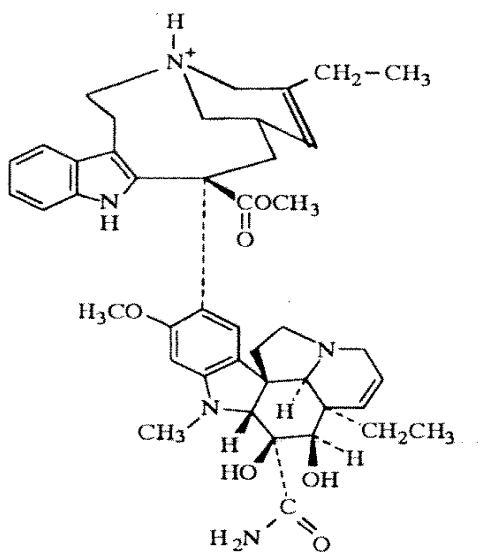
Mechanism: Similar to vincristine (inhibits tubulin polymerization); but also causes changes in amino acid metabolism principally involving glutamic acid and tryptophan.

Toxicity: Like vincristine but more myelosuppression (especially leukopenia). Leukopenia can be dose limiting and leukocyte counts are used to guide dosing.

ADME: Tri-phasic elimination with long terminal $t_{1/2}$ being ~24 hrs but this is shorter than vincristine; clearance mainly hepatic with involvement of CYP3A4. Use of strong inhibitors of CYP3A4 can increase peripheral neuropathy and myelosuppression.

Note(s): A natural product (di-alkaloid) initially isolated from the common Periwinkle plant.

Vinorelbine (Navelbine):



Uses: Non-small cell lung cancer, often with cisplatin. Administered IV only; intrathecal administration can be fatal. Vinca alkaloids are light sensitive.

Mechanism: Similar to vincristine but may also interfere with amino acid and glutathione metabolism, calmodulin-dependent Ca⁺⁺-transport, cellular respiration, nucleic acid biosynthesis and lipid biosynthesis.

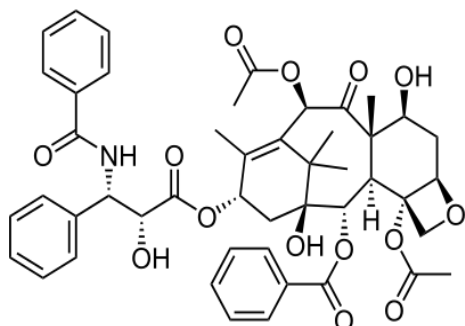
ADME: Tri-phasic elimination with long terminal $t_{1/2}$ being ~30 hrs; clearance mainly hepatic with involvement of CYP3A4. Use of strong inhibitors of CYP3A4 can increase myelosuppression and peripheral neuropathy.

Toxicity: Myelosuppression (especially granulocytopenia), peripheral neuropathy, constipation, paresthesia, alopecia; rare cases of interstitial pulmonary disease (IPD).

Note(s): A natural product (di-alkaloid) initially isolated from the common Periwinkle plant.

2. Taxanes (we will discuss 4)

Paclitaxel (Taxol): discovered in 1962 but initial approval not until 2001



Uses: Non-small cell lung cancer and ovarian cancer (with cisplatin), breast cancer (with doxorubicin and cyclophosphamide), prostate cancer (with prednisone). Administered IV only. Due to its very low aqueous solubility, this agent is formulated in a Cremophor/ethanol emulsion. Cremophor is polyethoxylated castor oil. However, this component can add complications (infusion reactions and unpredictable pharmacokinetics) to the use of this agent. Patients are premedicated with antihistamines and corticosteroids to reduce infusion reactions. (See Nab-Paclitaxel below.)

Mechanism: Binds to microtubules in the spindle apparatus and prevents their proper function. Specifically, it binds to microtubules and over-stabilizes them; opposite of vinca alkaloids.

Toxicity: Myelosuppression, peripheral neuropathy, alopecia. Myelosuppression can be worse when given with other agents (e.g. cisplatin), which also cause myelosuppression.

ADME: Bi-phasic elimination with terminal $t_{1/2}$ being ~10-20 hrs but dependent on dose*; clearance mainly hepatic with involvement of CYP2C8 mainly (CYP3A4 minor). Use of strong inhibitors (gemfibrozil) of CYP2C8 or inducers (rifampin) can increase myelosuppression and peripheral neuropathy. Paclitaxel (and other taxanes) have very high binding to serum albumin protein.

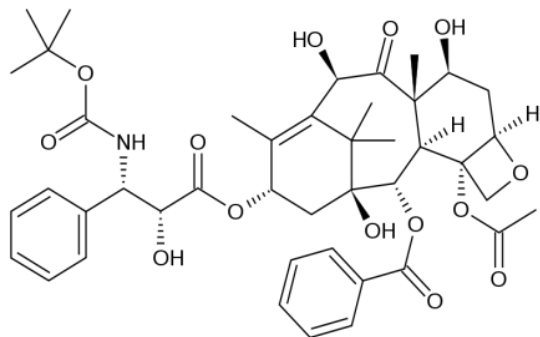
Note(s): *PK is complicated in part by the components of the formulation. Initially isolated from the Pacific Yew tree found in the Pacific Northwest; now it can be synthesized. Paclitaxel is a natural potent antifungal – of value to trees or shrubs in dark, damp forests.

Nab-Paclitaxel (Abraxane): approved in 2005

This is a relatively new formulation of paclitaxel. *Nab* stands for nanoparticle-albumin bound. This formulation utilizes human serum albumin to which paclitaxel (in nanoparticle form) is bound.

Uses: Breast cancer, pancreatic cancer in combination with gemcitabine; but no good reason it could not be used for everything that Taxol is used for. However, the cost is very high compared to Taxol which is generic.

Docetaxel (Taxotere):



Uses: Non-small cell lung cancer (with cisplatin), breast cancer (with doxorubicin and cyclophosphamide), prostate cancer (with prednisone), gastric cancer (with cisplatin and 5-FU), head and neck cancer squamous cell (with cisplatin and 5-FU). Due to its very low aqueous solubility, this agent is formulated in a polysorbate-80/ethanol solution. Polysorbate-80 (polyethoxylated sorbitan with oleic acid) is a non ionic surfactant and emulsifier. The PS-80 component can add complications (infusion reactions or hypersensitivity), similar situation to Cremophor.

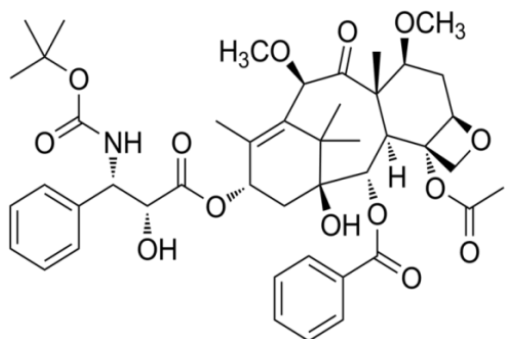
Mechanism: Binds to microtubules similar to paclitaxel but somewhat different binding. Also, the agent is somewhat more potent and more toxic than paclitaxel. Because the binding differs somewhat from that of paclitaxel, some patients can benefit after response to paclitaxel fails.

Toxicity: Myelosuppression, hepatotoxicity, peripheral neuropathy, hypersensitivity, alopecia.

ADME: Tri-phasic elimination with terminal t_{1/2} being ~10-15 hrs; clearance mainly hepatic and mainly by CYP3A4. Use of strong inhibitors of CYP3A4 can increase myelosuppression and peripheral neuropathy.

Note(s): Not a natural product – purely synthetic.

Cabazitaxel (Jevtana): approved June 2010



Uses: Prostate cancer (with prednisone) for patients that have been previously treated with docetaxel. Due to its very low aqueous solubility, this agent is formulated in a polysorbate-80/ethanol solution. The PS-80 component can add complications (infusion reactions or hypersensitivity).

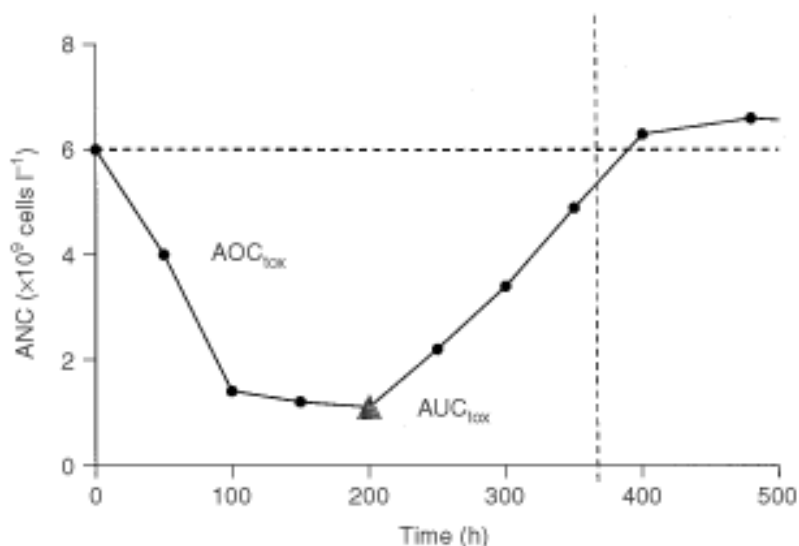
Mechanism: Similar to paclitaxel and docetaxel, but note the extreme similarity to docetaxel. This agent is also called dimethyl-docetaxel. More potent than either paclitaxel (P) or docetaxel (D). For example, doses: (P) 135-175 mg/m², (D) 60-100 mg/m², (C) 25 mg/m² all every 3 weeks (q3w) due to neutrophil nadir (Figure 2). Because it binds somewhat different to microtubules, it can sometimes overcome some drug resistance to P and D.

Toxicity: Myelosuppression, peripheral neuropathy, hypersensitivity, alopecia.

ADME: Tri-phasic elimination with very long terminal t_{1/2} being ~95 hrs; clearance is hepatic and mainly by CYP3A4. Use of strong inhibitors of CYP3A4 can increase myelosuppression and peripheral neuropathy. Poorer substrate for P-gp compared to P and D, therefore it is believed this agent is transported out of tissues and tumors less.

Note(s): Not a natural product – purely synthetic. Like docetaxel, it's a substrate of CYP3A4.

Figure 2. Illustration of the neutrophil drop and rise as a function of time

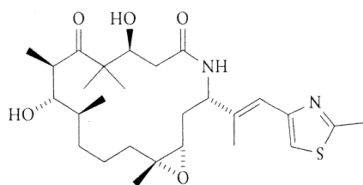


Myelosuppression is a common side effect of many anticancer agents, especially the antimetabolic agents. The specific loss of neutrophils is part of this suppression and neutrophils are very important for fighting infections and recovery of neutrophil counts can have an impact on dosing frequency. The nadir (low point) often occurs 7-14 days after dosing a chemotherapeutic. It can take up to 3 weeks for neutrophil counts to return to normal, or at least close to normal. Hence, dosing of anticancer agents that cause severe myelosuppression is often every 3 weeks (q3w).

21 days x 24 hrs/day = 504 hrs

3. Epothilones and halichondrins (we will discuss 2)

Ixabepilone (Ixempra): approved 2007



Uses: Breast cancer (commonly with capecitabine) for patients who have been previously treated with anthracyclines or who cannot tolerate additional anthracyclines. Or as monotherapy if a patient's tumor is resistant to anthracyclines, taxanes, or 5-FU. Administration is IV only. This drug is formulated similar to that of paclitaxel (Cremophor/ethanol). Therefore, infusion reactions and unpredictable pharmacokinetics can occur.* Patients should be premedicated with antihistamines and/or corticosteroids.

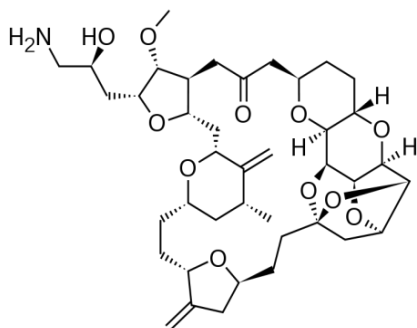
Mechanism: Similar to the taxanes in that it binds microtubules. However, the data indicate that the binding site(s) are quite different. Therefore, patients can often benefit after response to taxanes fail. Data indicate that ixabepilone is active in xenografts that are resistant to multiple agents including taxanes, anthracyclines, and vinca alkaloids. Ixabepilone has demonstrated synergistic antitumor activity in combination with capecitabine in vivo. In addition to direct antitumor activity by binding to microtubules, ixabepilone has antiangiogenic activity.

Toxicity: Peripheral neuropathy, myelosuppression, liver toxicity; *infusion and allergic reactions.

ADME: Long terminal t_{1/2} being ~50 hrs; clearance is hepatic and mainly by CYP3A4. Use of strong inhibitors of CYP3A4 can increase myelosuppression and peripheral neuropathy.

Note(s): Originally discovered as a defense compound in a bacterium that resides in soil.

Halichondrin (Eribulin, Halaven): approved Nov 2010



Uses: Breast cancer in patients who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. A patient's prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting. It is formulated as the mesylate salt (CH_3SO_4^-) which of course improves its water solubility.

Mechanism: Inhibits the growth phase (early phase) of microtubules leading to G2/M cell-cycle block.

Toxicity: Myelosuppression (especially neutropenia), peripheral neuropathy, alopecia, N/V, constipation. Some evidence of QT prolongation (see below).

ADME: Elimination $t_{1/2}$ of about 40 hrs; Eribulin is minimally metabolized and is excreted in the feces and urine mainly unchanged. Drug interactions with CYP enzymes are not an issue. Dosage adjustments are guided by blood cell counts and degree of peripheral neuropathy.

Note(s): Eribulin is a synthetic analogue of halichondrin B, a product isolated from the marine sponge *Halichondria okadai*.

QT prolongation: The QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. In general, the QT interval represents electrical depolarization and repolarization of the left and right ventricles. A lengthened QT interval is a biomarker for ventricular tachyarrhythmias (e.g. torsades de pointes) and a risk factor for sudden death*.

Starting in 2005, FDA and European regulators have required that nearly all new molecular entities are evaluated in a Thorough QT (TQT) study to determine a drug's effect on the QT interval. The TQT study serves to assess the potential arrhythmia liability of a drug.

*The QT interval is intrinsically longer in women than men.

Figure 3. The QT interval along with definitions of its components

