Anticancer drugs

79. MITOSIS INHIBITORS

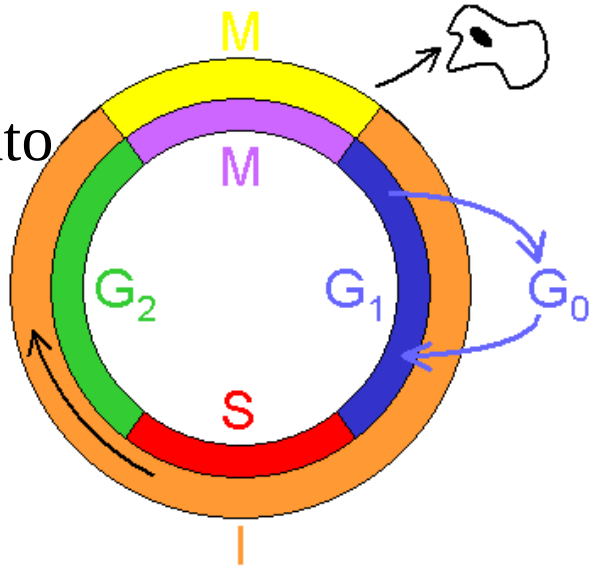
Mitosis is the process in which a eukaryotic cell separates the chromosomes in its cell nucleus into two identical sets in two daughter nuclei.

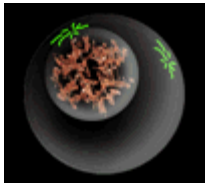
It is generally followed immediately by cytokinesis, which divides the nuclei, cytoplasm, organelles and cell membrane into two daughter cells containing roughly equal shares of these cellular components.

Mitosis and cytokinesis together define the **mitotic (M) phase** of the cell cycle - the division of the mother cell into two daughter cells, genetically identical to each other and to their parent cell.

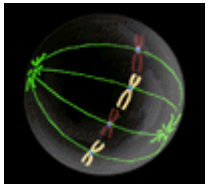
Mitosis

The M-phase of the cell cycle is subdivided into four sub-phases:

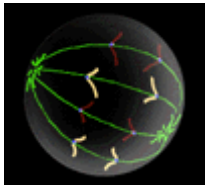




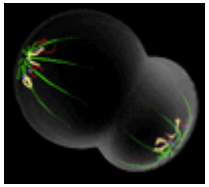
Prophase - nuclear membrane breaks down, mitotic spindle forms, chromosones condense



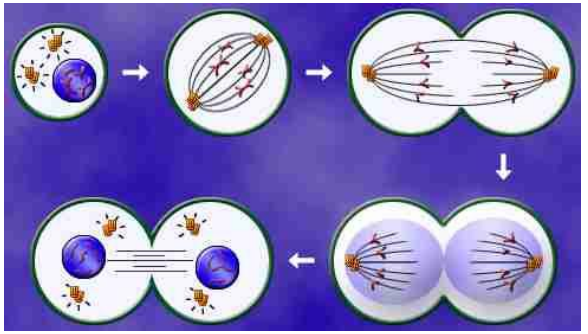
Metaphase - chromosones condense at equator



Anaphase - chromosones segment into chromatids and separate



Telophase - cell divides into parent and daughter cells



Some anticancer drugs act on cell nucleus division, which takes place before cell division.

Microtubules are the places where those drugs act in eucariotic cells. Microtubules are the cylindrical protein structures responsible for the creation of the spindle in the first phase of mitosis called prophase.

Microtubules are created as a result of association of tubulin proteins.
They are dimers consisting of two subunits.

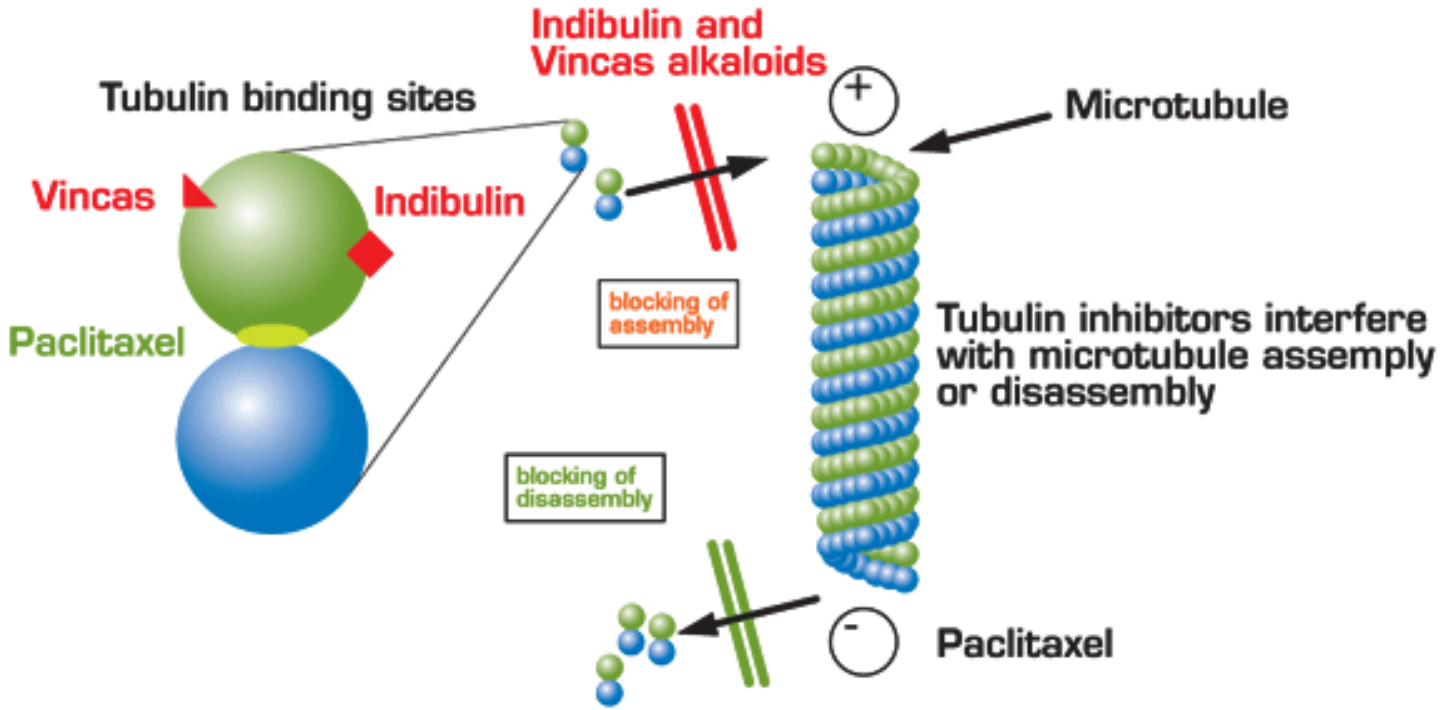
Some antimitosis drugs bind with different places in tubulin and inhibit mitosis in metaphase and some of them disturb the creation of microtubules.

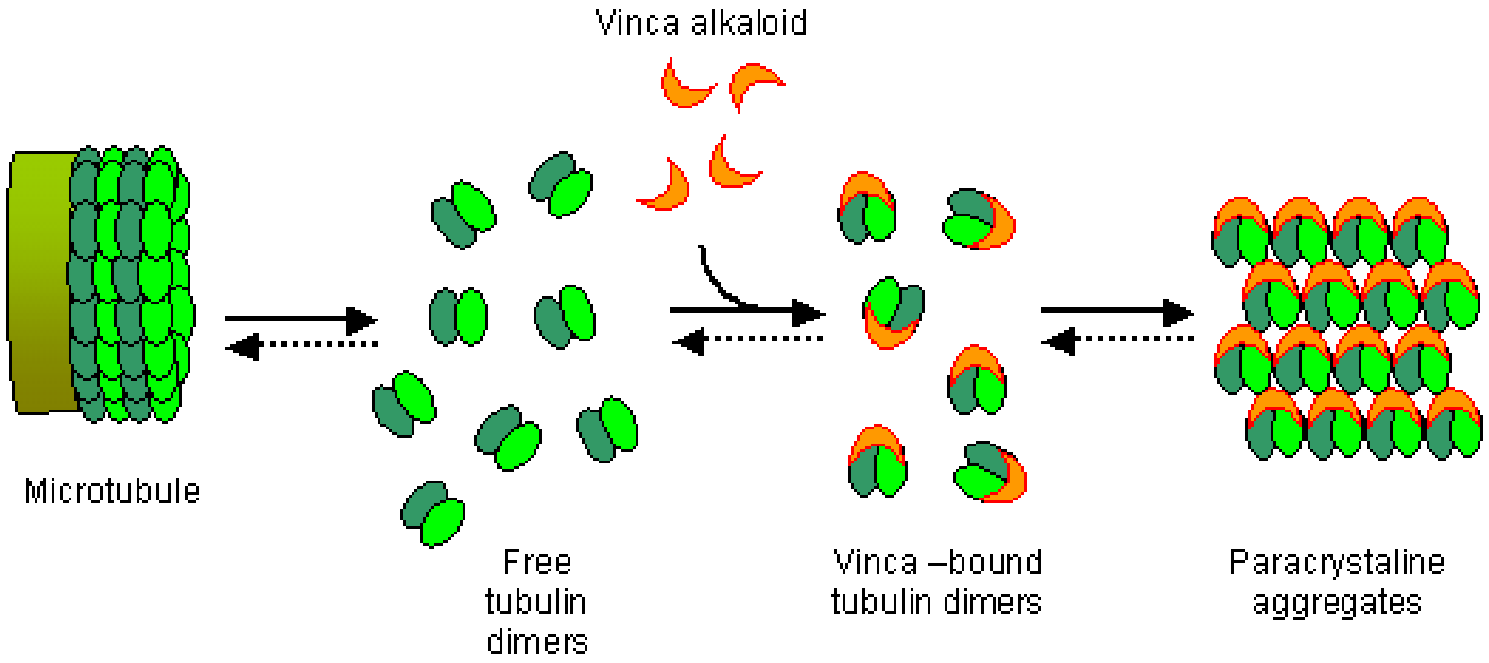
The following groups are recognized as antimitosis drugs:

- vinca alkaloids (Vinca rosea) – vinblastine, vincristine and a semisynthetic derivative – vindesine
- taxanes – paclitaxel and docetaxel
- epothilones

Modes of action

Antimitotics bind to tubulin and inhibit spindle dynamics and thus block cell division.




Vinca alkaloid
Microtubule
Free tubulin dimers
Vinca –bound tubulin dimers
Paracrystaline aggregates

C. roseus has gained interest from the pharmaceutical industry; the alkaloids vincristine and vinblastine from its sap have been shown to be an effective treatment for leukaemia and lymphoma.

Although the sap is poisonous if ingested, some 70 useful alkaloids have been identified from it.

In Madagascar, extracts have been used for hundreds of years in herbal medicine for the treatment of diabetes, as hemostatics and tranquilizers, to lower blood pressure, and as disinfectants.

The extracts are not without their side effects, however, which include hair loss.

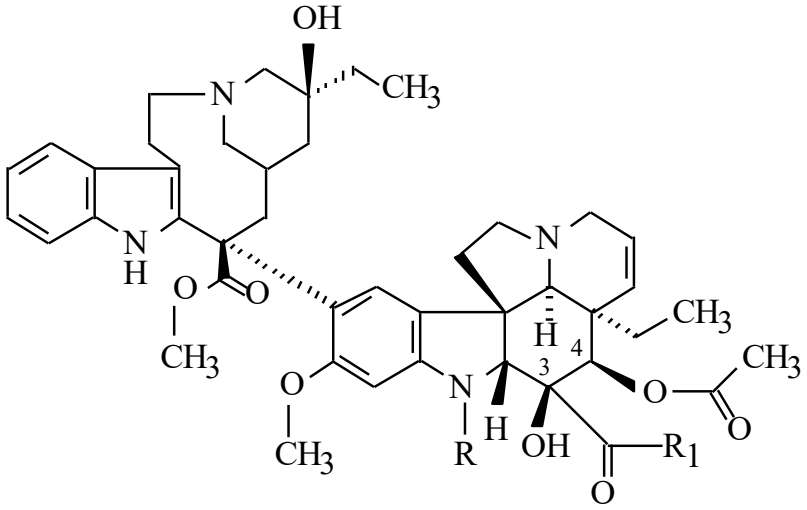
Catharanthus roseus

Vinca alkaloids are anti-mitotic and anti-microtubule agents.

They are nowadays produced synthetically and used as drugs in cancer therapy and as immunosuppressive drugs.

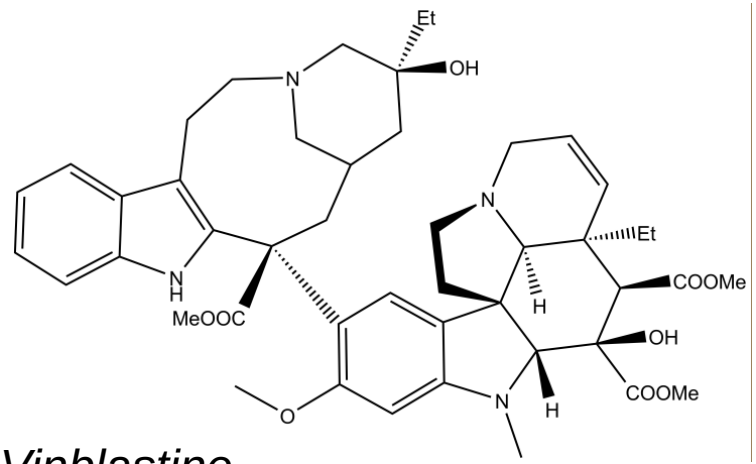
Periwinkle extracts and derivatives, such as vinpocetine, are also used as nootropic drugs.

Vinca alkaloids are dimers connected with indole and indoline groups.
The natural alkaloids – vinblastine and vincristine have differnt substituents at the nitrogen atom in the hydrated indole ring.



Vinblastine, R = -CH_3, R_1 = -OCH_3; VELBON
Vincristine, R = -CHO, R_1 = -OCH_3; ONCOVIN
Vindesine, R = -CH_3, R_1 = -NH_2; ELDESINE

Vinblastine and vincristine are characterised by triphase half-time, which is 4.5 min, 1.5 h and 28.5 h for vinblastine and 1 h, 3 h and 144 h for vincristine.



Vinblastine

Pharmacology

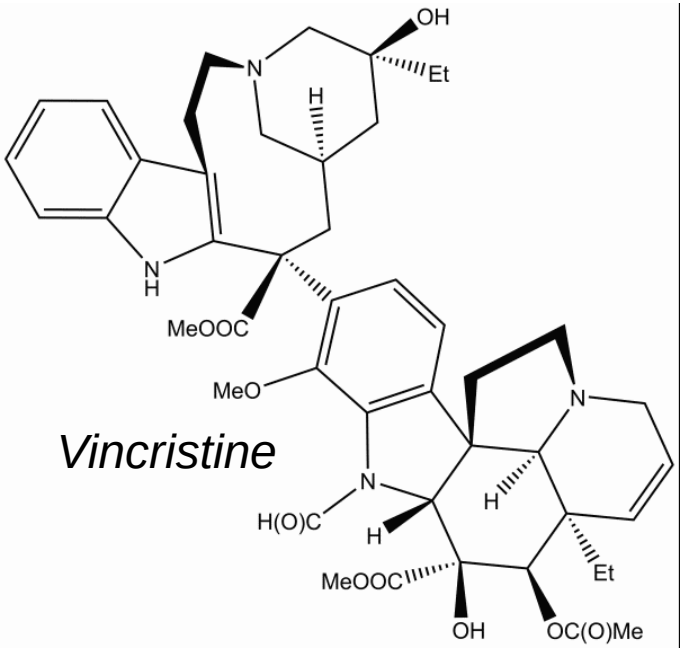
Vinblastine binds tubulin, thereby inhibiting the assembly of microtubules.
It is M phase cell cycle specific since microtubules are a component of the mitotic spindle and the kinetochore which are necessary for the separation of chromosomes during anaphase of mitosis.

Toxicities include bone marrow suppression (which is dose-limiting), gastrointestinal toxicity, potent vesicant (blister-forming) activity, and extravasation injury (forms deep ulcers).
Vinblastine paracrystals may be composed of tightly-packed unpolymerized tubulin or microtubules.

Indications

Vinblastine is a component of a number of chemotherapy regimens, including ABVD for Hodgkin lymphoma.

ABVD is a chemotherapy regimen used in the first-line treatment of Hodgkin lymphoma. It consists of concurrent treatment with the chemotherapy drugs adriamycin (doxorubicin), bleomycin, vinblastine and dacarbazine.



Vincristine

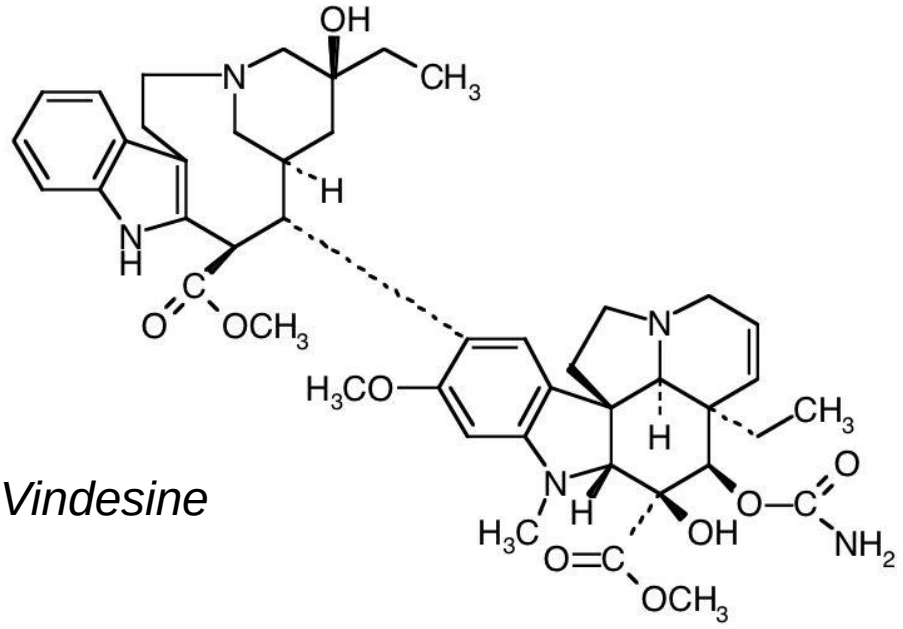
Uses

Vincristine is delivered via intravenous infusion for use in various types of chemotherapy regimens.
Its main uses are in non-Hodgkin's lymphoma as part of the chemotherapy regimen CHOP, Hodgkin's lymphoma as part of MOPP, COPP, BEACOPP, or the less popular Stanford V chemotherapy regimen, in acute lymphoblastic leukemia, and in treatment for nephroblastoma (Wilms tumor, a kidney tumor common in children).
Vincristine is occasionally used as an immunosuppressant, for example, in treating thrombotic thrombocytopenic purpura (TTP) or chronic idiopathic thrombocytopenic purpura (ITP).

Side effects

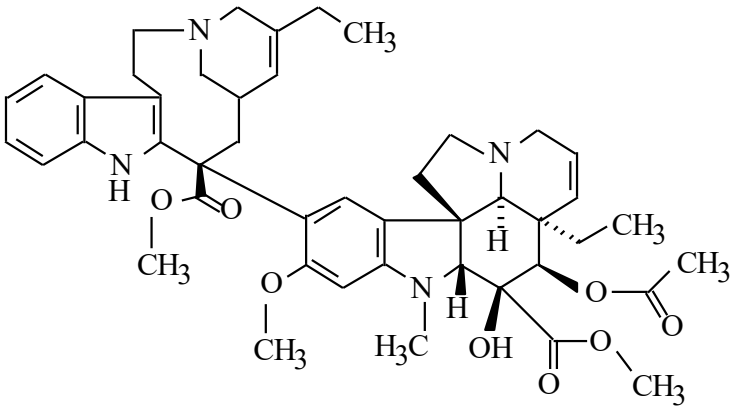
The main side-effects of vincristine are peripheral neuropathy, hyponatremia, constipation and hair loss.

Peripheral neuropathy can be severe, and hence a reason to avoid, reduce, or stop the use of vincristine. One of the first symptoms of peripheral neuropathy is foot drop: a person with a family history of foot drop and/or Charcot-Marie-Tooth disease (CMT) may benefit from genetic testing for CMT before taking vincristine.



Vindesine

Vindesine is used to treat many different types of cancer, including leukaemia, lymphoma, melanoma, breast cancer, and lung cancer.



Vinorelbine is the first 5´NOR semi-synthetic vinca alkaloid.

It is obtained by semi-synthesis from alkaloids extracted from the rosy periwinkle, *Catharanthus roseus*.

Vinorelbine, NAVELBINE

Vinorelbine (noranhydrovinblastine) is indicated in the treatment of inoperable breast carcinoma. Its end half-time is 40 h.

Vinorelbine has a number of side-effects that can limit its use:

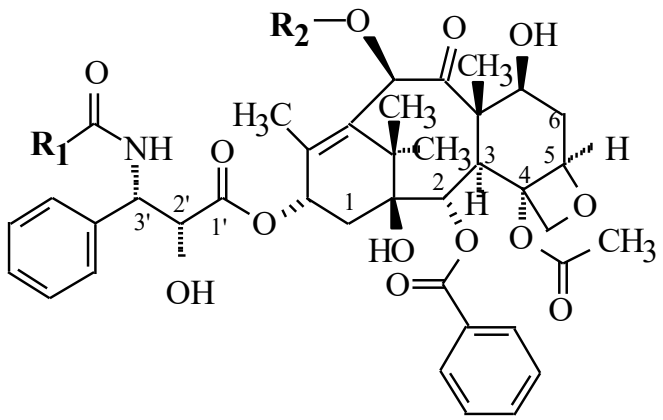
Lowered resistance to infection, bruising or bleeding, anaemia, constipation, diarrhoea, nausea, numbness or tingling in hands or feet (peripheral neuropathy), tiredness and a general feeling of weakness (asthenia), inflammation of the vein into which it was injected (phlebitis).
Seldom severe hyponatriamia is seen

Less common effects are hair loss and allergic reaction.

Taxanes

The **taxanes** are diterpenes produced by the plants of the genus *Taxus* (yews). As their name suggests, they were first derived from natural sources, but some have been synthesized artificially. Paclitaxel was originally derived from the Pacific yew tree.

Two drugs are now available:



Paclitaxel, R1 = -C_6H_5; R2 = Ac; TAXOL, PAXENE

Docetaxel, R1 = -O-$C(CH_3)_3$; R2 = H; TAXOTERE

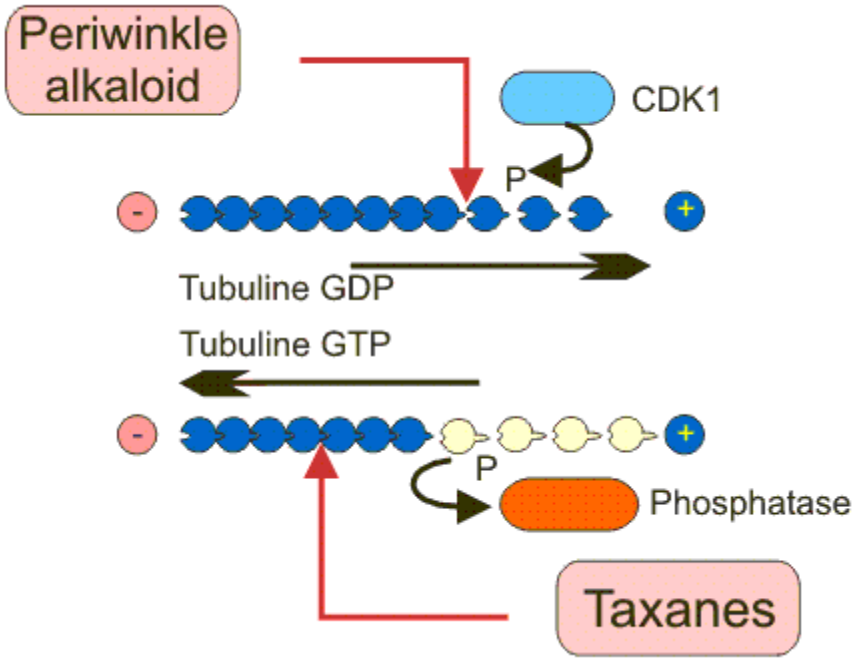
Larotaxel, Ortataxel and Tesetaxel are in clinical trials.

The taxane system and the side chain at C13 are responsible for the cytotoxic effects of taxanes.

Docetaxel differs from paclitaxel at two positions in its chemical structure.

It has a hydroxyl functional group on carbon 10, whereas paclitaxel has an acetate ester, and a tert-butyl carbamate ester exists on the phenylpropionate side chain instead of the benzyl amide in paclitaxel.

The carbon 10 functional group change causes docetaxel to be more water soluble than paclitaxel.



The mechanism of action

The principal mechanism of the taxane class of drugs is the disruption of microtubule function. It does this by stabilizing GDP-bound tubulin in the microtubule.

Microtubules are essential to cell division, and taxanes therefore stop this - a "frozen mitosis". Thus, taxanes are essentially mitotic inhibitors.

In contrast to the taxanes, the vinca alkaloids destroy mitotic spindles. Both, taxanes and vinca alkaloids are therefore named spindle poisons or mitosis poisons, but they act in different ways.

Paclitaxel - therapeutic applications

Paclitaxel is now used to treat patients with lung, ovarian, breast cancer, head and neck cancer, and advanced forms of Kaposi's sarcoma.

Paclitaxel is also used for the prevention of restenosis.

(**Restenosis** literally means the *re*occurrence of *stenosis*, a narrowing of a blood vessel, leading to restricted blood flow).

Taxol is weakly absorbed from the gastrointestinal tract.

After IV administration it binds with plasma proteins (90-95%).

Its half-time of elimination is 0.34 h and 4.9 h in phase beta.

Paclitaxel – adverse effects

Common side-effects include nausea and vomiting, loss of appetite, change in taste, thinned or brittle hair, pain in the joints of the arms or legs lasting 2–3 days, changes in the color of the nails, tingling in the hands or toes.

More serious side effects such as unusual bruising or bleeding, pain/redness/swelling at the injection site, change in normal bowel habits for more than 2 days, fever, chills, cough, sore throat, difficulty swallowing, dizziness, shortness of breath, severe exhaustion, skin rash, facial flushing and chest pain can also occur.

Dexamethasone is given prior to beginning paclitaxel treatment to mitigate some of the side effects.

Docetaxel

Docetaxel is a product of chemical modification of 10-deacetylbaccatin III, also present in the needles of the tree European yew (*Taxus baccata*).

Docetaxel does not have an acetyl group at position 10 of the ring but it has a modified side chain at position 13, which makes it different from paclitaxel.

Docetaxel

Its ability to bind with microtubules is many times greater than that of paclitaxel.

Docetaxel undergoes biotransformation in the liver and cytochrome P-450 participates in this process.

Alcohol aldehyde acid are the products of its oxidation.
The elimination of the drug is a triphase process (α, β, γ).
The values of $t_{1/2}$ are: 4 min, 36 min and 11.1 h for phases α, β and γ, respectively.

Docetaxel acts mainly in the S phase of the cell cycle.

Docetaxel – therapeutic applications

Docetaxel is a clinically well established anti-mitotic chemotherapy medication used mainly for the treatment of breast, ovarian, and non-small cell lung cancer.

Docetaxel has an approved claim for treatment of patients who have locally advanced, or metastatic breast or non small-cell lung cancer who have undergone anthracycline-based chemotherapy and failed to stop cancer progression or relapsed.

Administered as a one-hour infusion every three weeks generally over a ten cycle course, docetaxel is considered better than doxorubicin, paclitaxel and fluorouracil as a cytotoxic antimicrotubule agent.

Docetaxel – Adverse effects

Docetaxel is a chemotherapeutic agent and is a cytotoxic compound and so is effectively a biologically damaging drug.
As with all chemotherapy, adverse effects are common and many varying side-effects have been documented. Because docetaxel is a cell cycle specific agent, it is cytotoxic to all dividing cells in the body. This includes tumour cells as well as hair follicles, bone marrow and other germ cells. For this reason, common chemotherapy side effects such as alopecia occur; sometimes this can be permanent.

Haematological adverse effects include neutropenia (95.5%), anaemia (90.4%), febrile neutropenia (11.0%) and thrombocytopenia (8.0%). Deaths due to toxicity accounted for 1.7% of the 2045 patients and incidence was increased (9.8%) in patients with elevated baseline liver function tests (liver dysfunction).

Taxanes – Toxicity

Whereas their activities present great similarities, the toxicities of paclitaxel and docetaxel are somewhat different.

Both have a severe haematological toxicity essentially in the form of leukopenia.

They both provoke complete hair loss.

Paclitaxel has slowly progressing neurological toxicity with allergic phenomena which can be prevented by pre-medication.

Docetaxel provokes the progressive, dose related appearance of persisting oedema (first limited to lower limbs).

Pre-medication by corticosteroids reduces the incidence of this complication.

Epothilones

The **epothilones** are a new class of cytotoxic molecules identified as potential chemotherapeutic drugs. As of September 2008, epothilones **A** to **F** have been identified and characterised. Early studies in cancer cell lines and in human cancer patients indicate superior efficacy to the taxanes. Their mechanism of action is similar, but their chemical structure is simpler.

Due to their better water solubility, cremophors (solubilizing agents used for paclitaxel which can affect cardiac function and cause severe hypersensitivity) are not needed.
Endotoxin-like properties known from paclitaxel, like activation of macrophages synthesizing inflammatory cytokines and nitric oxide, are not observed for epothilone B.
Epothilones were originally identified as metabolites produced by the myxobacterium *Sorangium cellulosum.*

Several epothilone analogs are currently undergoing clinical development for treatment of various cancers. One analog, ixabepilone, was approved in October 2007 by the United States FDA for use in the treatment of aggressive metastatic or locally advanced breast cancer no longer responding to currently available chemotherapies. In November 2008, the EMEA has refused a marketing authorisation for Ixabepilone.

Epothilone B has proven to contain potent *in vivo* anticancer activities at tolerate dose levels in several human xenograft models. As a result, epothilone B and its various analogues are currently undergoing various clinical phases ([EPO906] and [SH-Y03757A, ZK-EPO, chemical structure] are in phase II trials; BMS-310704 and BMS-247550 in phase I trials).
Results of a phase III trial with ixabepilone in combination with capecitabine in metastatic breast cancer have been announced.

Epothilone B possess the same biological effects as taxol both *in vitro* and in cultured cells. This is because they share the same binding site, as well as binding affinity to the microtubule.

Like taxol, epothilone B binds to the αβ-tubulin heterodimer subunit. Once bound, the rate of αβ-tubulin dissociation decreases, thus stabilizing the microtubules. Furthermore, epothilone B has also been shown to induce tubulin polymerization into microtubules without the presence of GTP.

This is caused by formation of microtubule bundles throughout the cytoplasm. Finally, epothilone B also causes cell cycle arrest at the G2-M transition phase, thus leading to cytotoxicity and eventually cell apoptosis.