Plant alkaloids pharmacology

Plant alkaloids are anticancer agents derived from plants. These drugs act specifically **by blocking the ability of a cancer cell** to divide and become two cells. Although they act throughout the cell cycle, some are more effective during the S- and M- phases, making these drugs cell cycle specific.

Vinblastine

Vinblastine is an alkaloid derived from the periwinkle plant vinca rosea.

Its mechanism of action involves inhibition of tubulin polymerization, which disrupts the assembly of microtubules, an important part of the cytoskeleton and the mitotic spindle. This inhibitory effect results in mitotic arrest in metaphase, bringing cell division to a halt, which then leads to cell death.

Toxicity includes nausea and vomiting, bone marrow suppression, and alopecia. This agent is also a potent vesicant, and care must be taken in its administration.

It has clinical activity in the treatment of hodgkin's disease, non-hodgkin's lymphomas, breast cancer, and germ cell cancer.

Vincristine

Vincristine is an alkaloid derivative of vinca rosea and is closely related in structure to vinblastine. Its mechanism of action is considered to be identical to that of vinblastine in that it functions as a mitotic spindle poison leading to the arrest of cells in the m phase of the cell cycle. Despite these similarities to vinblastine, vincristine has a strikingly different spectrum of clinical activity and toxicity.

Vincristine has been effectively combined with prednisone for remission induction in acute lymphoblastic leukemia in children.

It is also active in various hematologic malignancies such as hodgkin's and non-hodgkin's lymphomas, and multiple myeloma, and in several pediatric tumors including rhabdomyosarcoma, neuroblastoma, ewing's sarcoma, and wilms' tumor.

The main dose-limiting toxicity is neurotoxicity, usually expressed as a peripheral sensory neuropathy, although autonomic nervous system dysfunction—with orthostatic hypotension, sphincter problems, and paralytic ileus—cranial nerve palsies, ataxia, seizures, and coma have been observed.

While myelosuppression can occur, it is generally milder and much less significant than with vinblastine. The other potential side effect that can develop is the syndrome of inappropriate secretion of antidiuretic hormone (siadh).

Vinorelbine

Vinorelbine is a semisynthetic vinca alkaloid whose mechanism of action is identical to that of vinblastine and vincristine, ie, inhibition of mitosis of cells in the m phase through inhibition of tubulin polymerization. This agent has activity in non-small cell lung cancer and in breast cancer. Myelosuppression with neutropenia is the dose-limiting toxicity, but nausea and vomiting, transient elevations in liver function tests, neurotoxicity.

Epipodophyllotoxins

Two compounds, vp-16 (etoposide) and a related drug, vm-26 (teniposide), are semisynthetic derivatives of podophyllotoxin, which is extracted from the mayapple root (podophyllum peltatum). Both an intravenous and an oral formulation of etoposide are approved for clinical use in the usa.

Etoposide and teniposide are similar in chemical structure and in their effects—they block cell division in the late s-g2 phase of the cell cycle. Their primary mode of action involves inhibition of topoisomerase ii, which results in dna damage through strand breakage induced by the formation of a ternary complex of drug, dna, and enzyme.

The drugs are water-insoluble and have to be formulated in a cremophor vehicle for clinical use. These agents are administered via the intravenous route and are rapidly and widely distributed throughout the body except for the brain. Up to 90–95% of drug is protein-bound, mainly to albumin.

Dose reduction is required in the setting of renal dysfunction. Etoposide has clinical activity in germ cell cancer, small cell and non-small cell lung cancer, hodgkin's and non-hodgkin's lymphomas, and gastric cancer and as high-dose therapy in the transplant setting for breast cancer and lymphomas. Teniposide use is limited mainly to acute lymphoblastic leukemia.

Camptothecins

The camptothecins are natural products that are derived from the camptotheca acuminata tree, and they inhibit the activity of topoisomerase i, the key enzyme responsible for cutting and religating single dna strands. Inhibition of the enzyme results in dna damage.

Topotecan is indicated in the treatment of advanced ovarian cancer as second-line therapy following initial treatment with platinum-based chemotherapy. It is also approved as second-line therapy of small cell lung cancer. The main route of elimination is renal excretion, and dosage must be adjusted in patients with renal impairment.

Irinotecan is a prodrug that is converted mainly in the liver by the carboxylesterase enzyme to the sn-38 metabolite, which is a potent inhibitor of topoisomerase i. In contrast to topotecan, irinotecan and sn-38 are mainly eliminated in bile and feces, and dose reduction is required in the setting of liver dysfunction. Irinotecan was originally approved as second-line monotherapy in patients with metastatic colorectal cancer who had failed fluorouracil-based therapy.

It is also approved as first-line therapy when used in combination with 5-fluorouracil and leucovorin.

Myelosuppression and diarrhea are the two most common adverse events. There are two forms of diarrhea: an early form that occurs within 24 hours after administration and is thought to be a cholinergic event effectively treated with atropine, and a late form that usually occurs 2–10 days after treatment. Late diarrhea can be severe, leading to significant electrolyte imbalance and dehydration in some cases.

Taxanes

Paclitaxel is an alkaloid ester derived from the pacific yew (taxus brevifolia) and the european yew (taxus baccata). The drug functions as a mitotic spindle poison through high-affinity binding to microtubules with the enhancement of tubulin polymerization. This promotion of microtubule assembly by paclitaxel occurs in the absence of microtubule-associated proteins and guanosine triphosphate and results in inhibition of mitosis and cell division.

Paclitaxel has significant activity in a broad range of solid tumors, including ovarian, advanced breast, non-small cell and small cell lung, head and neck, esophageal, prostate, and bladder cancers and aids-related kaposi's sarcoma. It is metabolized extensively by the liver p450 system, and nearly 80% of the drug is excreted in feces via the hepatobiliary route.

Hypersensitivity reactions may be observed in up to 5% of patients, but the incidence can be reduced by premedication with dexamethasone, diphenhydramine, and an h2 blocker.

A novel albumin-bound paclitaxel formulation (Abraxane) has recently been approved for use in metastatic breast cancer. In contrast to paclitaxel, this formulation is not associated with hypersensitivity reactions, and premedication to prevent such reactions is not required. Moreover, this agent has significantly reduced myelosuppressive effects compared with paclitaxel, and the neurotoxicity that results appears to be more readily reversible than is typically observed with paclitaxel.

Docetaxel is a semisynthetic taxane derived from the European yew tree. Its mechanism of action, metabolism, and elimination are identical to those of paclitaxel. It is approved for use as second-line therapy in advanced breast cancer and non-small cell lung cancer, and it also has major activity in head and neck cancer, small cell lung cancer, gastric cancer, advanced platinum-refractory ovarian cancer, and bladder cancer.