Pharmacological Activity of Vinca Alkaloids

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ABSTRACT

Vinca alkaloids are a set of drugs obtained from the periwinkle plant. They are naturally extracted from the plant *Catharanthus roseus*, and have hypoglycemic and cytotoxic effects. These are used to treat diabetes, high blood pressure and are also used as disinfectants. The vinca alkaloids are important as they can fight against cancer. The four major vinca alkaloids having medicinal properties are: Vinblastine (VBL), vinorelbine (VRL), vincristine (VCR) and vindesine (VDS). Vinflunine is a new synthetic vinca alkaloid, which has been approved in Europe for the treatment of second-line transitional cell carcinoma of the urothelium. Vinca alkaloids are the second-most-used class of cancer drugs.

INTRODUCTION

*Catharanthus roseus* is generally known as Madagascar periwinkle and belongs to the family Apocynaceae. It is cultivated for its herbal use and as ornamental plant (Figure 1). Alkaloids are set of organic compounds made up of carbon, hydrogen, nitrogen and oxygen and are derived from plant. Vinca alkaloids are the oldest group of the plant alkaloid groups that used to treat cancer [1-7].

Vinca alkaloids were discovered in the 1950’s by Robert Noble and Charles Beer of Canada. Medicinal uses of this plant led to the monitoring of its compounds for their hypoglycemic activity and cytotoxic effect. These are used to treat diabetes, high blood pressure and also used as disinfectants. However, vinca alkaloids are of main importance due to their cancer fighting ability [8-14]. The four major vinca alkaloids having medicinal use are: Vinblastine, vinorelbine, vincristine and vindesine, but only Vinblastine, vinorelbine, vincristine are approved for use in the United States. There also exists a novel vinca alkaloid, vinflunine that is currently approved in Europe for medicinal treatment [15-19].
MECHANISM OF ACTION

The vinca alkaloid cytotoxicity is due to the synergy with tubulin and disruption of microtubule function. This occurs mainly in the microtubules comprising the mitotic spindles, causing the arrest of metaphase (Figure 2A and 2B) [20-26]. There are many other biochemical activities of these alkaloids that may or may not be related to their effect on microtubules. After the treatment of the cells with doses of vinca alkaloids, there doesn't show any effect on the microtubules. Vinca alkaloids and other antimicrotubule agents have effect on non-malignant as well as malignant cells in the non-mitotic cell division, because microtubules are involved in many non-mitotic functions.

Vinca alkaloids bind to the receptor sites on tubulin and separate from the taxanes, colchicine, podophyllotoxin and guanosine-5’-triphosphate. Binding occurs rapidly as well as slowly. There exist two vinca alkaloid binding sites per mole of tubulin dimer. There are 16-17 high-affinity binding sites that are located at the end of the microtubule. Binding of the vinca alkaloids to the binding site of tubulin interrupts microtubule segregation, but one of the most important effects of low drug concentration of vinca alkaloid is decrease growth rate and shortening at the assembly end of the microtubule, which cause a “kinetic cap” and suppresses function (Figure 3) [26-33].

Vinca alkaloids inhibit malignant angiogenesis in vitro. For example, Vinblastine with concentrations of 0.1 to 1.0 pmol/L blocks endothelial proliferation, chemotaxis and spreading on fibronectin but other fibroblasts and lymphoid tumors remain unaffected at these low concentrations [34-42]. Low doses of Vinblastine in combination with antibodies against vascular endothelial growth factor increase antitumor response even in tumors resistant to direct cytotoxic effects of drug. Vincristine and related compounds produce destabilization of microtubules by binding to tubulin and blocking the polymerization.

MEDICINAL USES AND TOXICITY

Vinca alkaloids are generally used in combination chemotherapy regimens for medicinal therapies. They do not have cross-resistance with drugs that alkylate DNA and whose mechanism of action is different. Vinblastine is

Figure 2. A) Normal mitosis; B) Mitosis blocked by vinca alkaloids.
used in medicinal treatment for testicular carcinoma, Hodgkin Lymphoma and Non-Hodgkin lymphoma. It is also used in curing of breast cancer and germ cell tumors. Side-effects of Vinblastine include nausea, vomiting, constipation, toxicity to white blood cells, dyspnea, chest pain, wheezing and fever. It is rarely associated in the secretion of antidiuretic hormone[43-48].

Vinorelbine is similar to Vinblastine. It has antitumor activity against breast cancer and can be affective against bone tumor cells, osteosarcoma. In addition, Vinorelbine decreases the stability of lipid bilayer membranes. Side-effects of Vinorelbine include decreased resistance to infection, bleeding, anemia, constipation, diarrhea, nausea, numbness or tingling in the hands and feet, fatigue and inflammation at the injection site[49-53].

Vincristine is used to treat acute leukemia, rhabdomyosarcoma, neuroblastoma, Wilm's tumor, Hodgkin's disease and other lymphomas. Vincristine is also used for treating several non-malignant hematologic disorders. The most common side-effects of Vincristine are peripheral neuropathy, bone marrow activity suppression, constipation, toxicity of nervous system, nausea and vomiting[54-67].

Vindesine is similar to Vinblastine in pharmacological activity. Vindesine also possess Antineoplastic activity and is seen in acute lymphocytic leukemia, chronic myeloid leukemia, malignant melanoma, pediatric solid tumors and metastatic renal, breast, esophageal and colorectal carcinomas[68-74]. A new synthetic vinca alkaloid was developed through the addition of two fluorine molecules by super acidic chemistry and is named as Vinflunine (Figure 4). Vinflunine is the first fluorinated inhibitor of microtubule that belongs to vinca alkaloids. Vinflunine is used in Europe for the treatment of second-line transitional cell carcinoma of the urothelium (TCCU)[75-83].
Vinca alkaloids are quite similar in structure (Figure 5) but their toxicologic profiles are extensively different. All vinca alkaloids produce peripheral neurotoxicity, but Vincristine is more potent compared to other vinca alkaloids [84-89]. The primary pathological effect of vinca alkaloids is axonal degeneration. The uptake of Vincristine into the brain is low and there also observed infrequent central nervous system effects, such as confusion, mental status changes, depression, hallucinations and visual disturbances. Laryngeal paralysis was also reported at times. The only effective way to reduce neurotoxicity caused by vinca alkaloid is by discontinuing treatment or by decreasing the dose and dosing frequency. Neutropenia is the main dose-limiting toxicity of Vinblastine, Vindesine and Vinorelbine. Thrombocytopenia and anemia rarely reported. Vincristine rarely causes hematologic toxicity; severe myelosuppression has been monitored in situations resulting in profoundly increased drug exposure and hepatic deficiency [90-94].

![Vinblastine](image1)
![Vincristine](image2)
![Vindesine](image3)
![Vinorelbine](image4)

**Figure 5.** Structural formula of major Vinca alkaloids: Vinblastine, Vincristine, Vindesine, Vinorelbine.

Gastrointestinal toxicities may be observed with the usage of vinca alkaloids. Vincristine or high doses of the other vinca alkaloids cause gastrointestinal autonomic dysfunction which includes constipation, ileus and abdominal pain. Mucositis occurs more frequently with Vinblastine than Vinorelbine and is common with Vincristine. Nausea, vomiting and diarrhea were also reported.

The vinca alkaloids are effective vesicants and these may lead to tissue damage also. Acute cardiac ischemia, chest pains without ischemia, fever without an obvious source, acute pulmonary effects, Raynaud phenomenon have also been reported with the use of vinca alkaloids [95-97].

Vinca alkaloids are contraindicated during pregnancy, have been planning for pregnancy or during breast-feeding as it may cause birth abnormalities. Patients should not receive any vaccinations while taking this medication. Vincristine may also cause weakness of immunity system and can lead to an illness. Patients should notify their clinician in prior about any prescription drugs taken concurrently and also suffering with any other medical conditions, such as, herpes zoster infection, gout, kidney stones, chickenpox, infections, liver disease, nerve or muscle disease [98-100]. However, the drug concentration and treatment duration are of main importance for determining drug accumulation and cytotoxicity.
CONCLUSION

Vinca alkaloids are generally used in Chemotherapy of Cancer. They do not have cross-resistance with drugs that alkylate DNA. They are used to treat diabetes, high blood pressure, etc. These are also used as disinfectants. Vinca alkaloids have cytotoxic effect that arrests the cell division and finally causes death of the cells. The four major vinca alkaloids used clinically are Vinblastine, Vinorelbine, Vincristine and Vindesine. Vinflunine is a synthetic vinca alkaloid which has been in use recently for the treatment of second-line transitional cell carcinoma of the urothelium and other malignancies. Overall, vinca alkaloids are the second most-used class of cancer drugs. Different researches and studies for new vinca alkaloid applications are being carried out in this regard.

REFERENCES


