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Vinca Alkaloids

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ABSTRACT

Vinca alkaloids are a subset of drugs obtained from the Madagascar periwinkle plant. They are naturally extracted from the pink periwinkle plant, Catharanthus roseus G. Don and have a hypoglycemic as well as cytotoxic effects. They have been used to treat diabetes, high blood pressure and have been used as disinfectants. The vinca alkaloids are also important for being cancer fighters. There are four major vinca alkaloids in clinical use: Vinblastine (VBL), vinorelbine (VRL), vincristine (VCR) and vindesine (VDS). VCR, VBL and VRL have been approved for use in the United States. Vinflunine is also a new synthetic vinca alkaloid, which has been approved in Europe for the treatment of second-line transitional cell carcinoma of the urothelium is being developed for other malignancies. Vinca alkaloids are the second-most-used class of cancer drugs and will stay among the original cancer therapies. Different researches and studies for new vinca alkaloid applications will be carried out in this regard.

Keywords: Madagascar periwinkle, vinblastine, vinca alkaloids, vincristine, vindesine, vinflunine, vinorelbine

Review Article

INTRODUCTION

What are vinca alkaloids?

Vinca alkaloids are a material of a class of organic compounds made up of carbon, hydrogen, nitrogen and oxygen that is often derived from plants is named alkaloid. Although, the name represents alkali like some do not exhibit alkaline properties. Many alkaloids with having poisonous characteristics have physiological effects too that make them useful as medicines.[1] The oldest group of the plant alkaloids groups that used to treat cancer are the vinca alkaloids.[2]

Vinca alkaloids are obtained from the Madagascar periwinkle plant. They are naturally occurring or semi synthetic nitrogenous bases extracted from the pink periwinkle plant *Catharanthus roseus* G. Don[3] [Figure 1]. Vinca alkaloids were found out in the 1950's by Canadian scientists, Robert Noble and Charles Beer for the first time. Medicinal applications of this plant lead to the monitoring of these compounds for their hypoglycemic activity, which is of little importance compared to their

Figure 1: The flowers of *Catharanthus roseus* G. Don. Catharanthus roseus (syn. Vinca rosea) an evergreen shrub, it grows to a height of 1 m with a spread of 1 m. The stem is short, erect and branching; the leaves are glossy green, oval, 5 cm long and opposite acuminate; the flowers are soft pink, tinged with red, 5 petal, open, tubular and 4 cm across, appearing in spring and autumn (three colors: pink, purple and white) (http://my.opera.com/Thachthaotim84/albums/showpic.dml)

cytotoxic effects.[4] They have been used to treat diabetes, high blood pressure and the drugs have even been used as disinfectants. Nevertheless, the vinca alkaloids are so important for being cancer fighters. There are four major vinca alkaloids in clinical use: Vinblastine (VBL), vinorelbine (VRL), vincristine and vindesine (VDS), but only VCR, VBL and VRL are approved for use in the United States.[3] From 2008, there is also a new synthetic vinca alkaloid, vinflunine that is currently approved in Europe for medicinal treatment.[5,6]

MECHANISM OF ACTION

The main mechanisms of vince alakaloid cytotoxicity is due to their interactions with tubulin and disruption of microtubule function, particularly of microtubules comprising the mitotic spindle apparatus, directly causing metaphase arrest.[7] However, they can do many other biochemical activities that may or may not be related to their effects on microtubules. Many of the effects that do not include microtubule interruption happen only after treatment of cells with clinically irrelevant doses of the vinca alkaloids. Nevertheless, the vinca alkaloids and other antimicrotubule agents also have an effect on both non-malignant and malignant cells in the non-mitotic cell cycle, because microtubules are involved in many non-mitotic functions.[3]

The vinca alkaloids connect to binding sites on tubulin that they are separate from those of the taxanes, colchicine, podophyllotoxin and guanosine-5'-triphosphate.[8] Binding occurs rapidly and can reverse too. Existing evidence maintains the existence of two vinca alkaloid binding sites per mole of tubulin dimer.[9] We can see near to 16-17 high-affinity binding sites in each microtubule that located at the ends of per microtubule. Binding of the vinca alkaloids to these sites interrupts microtubule congregation, but one of the most important effect of low drug concentrations can be decreasing the rates of both growth and shortening at the assembly end of the microtubule that can cause produces a "kinetic cap" and suppresses function.[10] The disturbing effects of the vinca alkaloids on microtubule dynamics, particularly at the ends of the mitotic spindle, which cause metaphase arrest, occur at drug concentrations below those that decrease microtubule mass.[11]

The vinca alkaloids and other microtubule disrupting agents have power to inhibit malignant angiogenesis *in vitro*. For example, VBL with concentrations range from 0.1 to 1.0 pmol/L blocked endothelial proliferation, chemotaxis and spreading on fibronectin, all essential steps in angiogenesis,[12] but other normal fibroblasts and lymphoid tumors were unaffected at these minute concentrations. In combination with antibodies against vascular endothelial growth factor, low doses of VBL increased antitumor response considerably, even in tumors resistant to direct cytotoxic effects of the drug.[13] Vinca alkaloids inhibit cell proliferation by binding to microtubules, which can cause a mitotic block and apoptosis. VCR and related compounds produce destabilization of microtubules by binding to tubulin and blocking the polymerization.[14]

MEDICINAL USES

The vinca alkaloids have been generally included in combination chemotherapy regimens

for medicinal therapies. They do not have cross-resistance with drugs that alkylate deoxyribonucleic acid (DNA) and have a different mechanism of action.[3] VBL has been used as an integral part of medicinal treatment regimens for testicular carcinoma and both Hodgkin and non-Hodgkin lymphomas.[15] It is also used in breast cancer and germ cell tumors. Side-effects of VBL consist of toxicity to white blood cells, nausea, vomiting, constipation, dyspnea, chest or tumor pain, wheezing and fever. It is also rarely associated with antidiuretic hormone secretion.[3]

VRL is same to VBL. It has significant antitumor activity in patients with breast cancer and can be affected on bone tumor cells, osteosarcoma. In addition, VRL decreases the stability of lipid bilayer membranes. In the United States, VRL has been approved for the initial treatment of patients with advanced lung cancer.[16] VRL's side-effects are: Decreasing resistance to infection, bruising or bleeding, anemia, constipation, diarrhea, nausea, numbness or tingling in the hands and feet, fatigue (also called peripheral neuropathy) and inflammation at the injection site. Less common side-effects include hair loss and allergic reaction.[3]

VCR has been approved to treat acute leukemia, rhabdomyosarcoma, neuroblastoma, Wilm's tumor, Hodgkin's disease and other lymphomas. Another characteristic of VCR that has been reported is treating several non-malignant hematologic disorders such as refractory autoimmune thrombocytopenia, hemolytic uremic syndrome and thrombotic thrombocytopenia purpura. VCR's most common side-effects are: Peripheral neuropathy, suppression of bone marrow activity, constipation, nervous system toxicity, nausea and vomiting.[3,15]

VDS has similar effects to VBL. Antineoplastic activity of VDS has been reported in acute lymphocytic leukemia, blast crisis of chronic myeloid leukemia, malignant melanoma, pediatric solid tumors and metastatic renal, breast, esophageal and colorectal carcinomas.[17] Recently, a new synthetic vinca alkaloid, vinflunine was developed through the addition of two fluor molecules by superacidic chemistry.[6] Vinflunine is the first fluorinated microtubule inhibitor that belongs to the vinca alkaloids. This compound has been used in Europe for the treatment of second-line transitional cell carcinoma of the urothelium (TCCU), is being developed for other malignancies. It has been applied for clinical development in the wide spectrum of solid tumors. Clinically, important activity has been seen mainly in the treatment of transitional cell carcinoma of the urothelial tract, non-small cell lung cancer and carcinoma of the breast. Vinflunine is has been also assessed in patients with TCCU and first-line advanced breast cancer.[5]

TOXICITY

Although, the vinca alkaloids are quite similar from a structural position, their toxicologic profiles are different extensively. All vinca alkaloids make a characteristic peripheral neurotoxicity, but VCR has most potential in this case. The neurotoxicity is mostly distinguished by a peripheral, symmetric varied sensory-motor and autonomic polyneuropathy.[7] The primary pathologic effect is related to axonal degeneration and decreasing of axonal transport, most likely caused by a drug-induced perturbation of microtubule function. The uptake of VCR into the brain is low and central nervous system effects, such as confusion, mental status changes, depression, hallucinations, agitation, insomnia, seizures, coma, syndrome inappropriate secretion of antidiuretic hormone and visual disturbances are infrequent. Laryngeal paralysis has also been informed. The only known effective interference for vinca alkaloid neurotoxicity is discontinuing treatment or decrease of the dose or frequency of drug administration. Although a number of antidotes, including thiamine, vitamin B_{12}, folinic acid, pyridoxine and neuroactive agents, have been applied, these treatments have not been obviously shown to be effective. The symptoms of neurotoxicity are similar for all vinca alkaloids; severe neurotoxicity is observed less frequently with VBL and VRL as compared with VCR. Neutropenia is the main dose-limiting toxicity of VBL, VDS and VRL. Thrombocytopenia and anemia usually have been seen less. In addition, VCR is related with hematologic toxicity rarely, severe myelosuppression has been monitored in situations resulting in profoundly increased drug exposure and hepatic deficiency.[3]

Gastrointestinal toxicities, aside from those caused by autonomic dysfunction, may be observed

with using vinca alkaloids.[18] Gastrointestinal autonomic dysfunction, as manifested by bloating, constipation, ileus and abdominal pain, occur most commonly with VCR or high doses of the other vinca alkaloids. Mucositis occurs more frequently with VBL than VRL and is common with VCR. Nausea, vomiting and diarrhea may also occurred. The vinca alkaloids are effective vesicants and may lead to significant tissue damage too.[3] Acute cardiac ischemia, chest pains without evidence of ischemia, fever without an obvious source, acute pulmonary effects, Raynaud phenomenon, Hand-foot syndrome and pulmonary and hepatic toxicity have also been seen with the vinca alkaloids.[19]

These drugs should not be used by a patient who is pregnant, has planning for pregnancy or has breast-feeding as it may cause birth defects. Patients should not receive any vaccinations while taking this medication. VCR may cause weakness of immunity system and can lead to an illness.[20] Patients should notify their clinician about any prescription drugs taken concurrently with the chemotherapy and any other medical conditions, such as, chickenpox, herpes zoster infection, gout, kidney stones, infections, liver disease, nerve or muscle disease.[20] Over all, drug concentration and duration of treatment are important for determining of both drug accumulation and cytotoxicity, but the importance of available information show that using of drug above a critical threshold concentration is the most important determinant.[21]

CONCLUSIONS

Vinca alkaloids have been generally included in combination chemotherapy regimens for medicinal therapies. They do not have cross-resistance with drugs that alkylate DNA and have a different mechanism of action. They have been used to treat diabetes, high blood pressure and have been used as disinfectants and anti-cancer. The vinca alkaloids have cytotoxic effects that can arrest the division of cells and causes cell death. There are four major vinca alkaloids in clinical use: VBL, VRL, VCR and VDS. VCR, VBL and VRL have been approved for use in the United States. Vinflunine is also a new synthetic vinca alkaloid, which has been approved in Europe for the treatment of second-line TCCU, is being developed for other malignancies. Overall, vinca alkaloids have the second most-used class of cancer drugs and will stay among the original cancer therapies. Different researches and studies for new vinca alkaloid applications will be carried out in this regard.

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