# A Comprehensivereview of vincristine – A Vinca alkaloid used for treatment of chemotherapy and its importance

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***Abstract*- Vincristine is a chemotherapeutic agent obtained from natural alkaloid plant source Catharanthus roseus. Vincristine has been significantly useful in treatments of lung cancer.lymphocyte based leukaemia, glioblastomas and acute myeloid leukaemia, glioblastomas and acute myeloid leukaemia.Vincristine possesses low cancer tissue affinity and at higher dose often led to irreversible neurotoxicity. vincristine attaches the tubulin fibrils and prevents filaments polymerization that permanently led to mitotis inhibition in cancer cells.In this review ,we have summarized the chemotherapeutic role of vincristine and it's mechanism of action , importance in cancer prevention associated with vincristine delivery .Moreover , application of vincristine and effect on anticancer efficacy are also being discussed.**

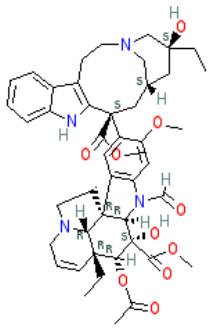
***Key words*- Vincristine, chemotherapy, alkaloids, cancer.**

## I. INTRODUCTION

The vinca alkaloid vincristine was first isolated from the medicinal herb found in Madagascar known as Catharanthus roseus. This cytotoxic drug was first discovered in 1985 and found useful in cancer therapy. VCR is also referred to as leurocristine and promoted commercially as "Oncovin". It is administered intravenously as chemotherapeutic agent for management of various type of melanomas including lung cancer, lymphocyte-based leukaemia, glioblastomas and acute myeloid leukaemia.

IUPAC NAME

methyl(1R,9R,10S,11R,12R,19R)-11-acetyloxy-12-ethyl-4-[(13S,15S,17S)-17-ethyl-17-hydroxy-13-methoxycarbonyl-1,11-diazatetracyclo[13.3.1.04,12.05,10]nonadeca-4(12),5,7,9-tetraen-13-yl]-8-formyl-10-hydroxy-5-methoxy-8,16-diazapentacyclo[10.6.1.01,9.02,7.016,19]nonadeca-2,4,6,13-tetraene-10-carbox

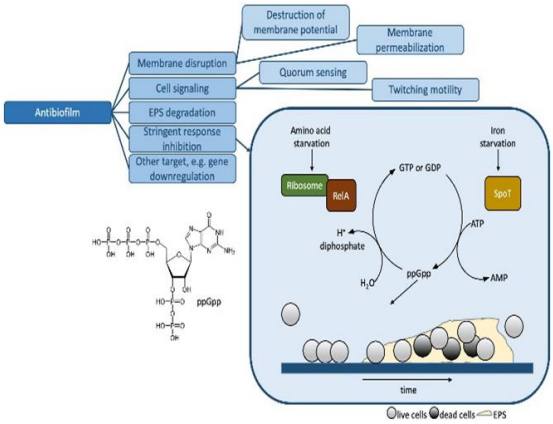


Chemistry of vincristine

VCR extracted from Catharanthus roseous (family Apocynaceae) which is a terpenoid indole alkaloid. It is isolated via semi-synthetic coupling of indole alkaloids vindoline and catharanthine. The molecular weight of VCR is Natural source and chemical 2D and 3D structure of vincristine 824.958 Da and its molecular formula is C46H56N4O10 VCR is synthesized using stereochemistry-driven mechanism for specific stereo selective at C2 and C18 in structure. The stereo selective carbons are essential for cytotoxic activity of VCR. To enhance the cytotoxicity, different functional groups are introduced in the structure. In vindoline structure acetyl group at C4 and hydroxyl group at C2 position is important. Loss of these groups leads to reduction in anticancer activity. Similarly, hydrogenation or reduction at C6-7 position at VCR also diminishes oncolytic process in cancer cells. The vincristine has low aqueous solubility of 0.03 mg/mL, pKa of 10.85 and 3.36 log p value

## II. MECHANISM OF ACTION

The physiological pathway of VCR initiates by arresting metaphase of mitosis in cell cycle. In metaphase, polymerization of tubulin protein forms filament microtubules that enables cell detachment from chromosomes and enter the next phase of cell development. It mainly arrests polymerization of dimer tubulin protein which subsequently initiates apoptosis in cells. Along apoptosis, VCR also suppresses the growth and production of leukocytes from bone marrow. However, lower dose exposure or high clearance leads to reversible binding of VC with tubulin protein. Therefore, the antitumor efficacy is dependent on dose and time of exposure. It is also reported to have anti-angiogenesis and apoptosis induction activity in 1 3 Drug Delivery and Translational Research. Vincristine mechanism of action on microtubule arrest for cancer cell cycle inhibition cancer cells. VCR can induce the calcium ion ATPase activity, lipid and nucleic acid formation, and cell respiration. Its hypoglycaemic effect is well studied and further reported in preclinical research. The standard dose of vincristine is 1–1.4 mg/m2 every 3 weeks (intravenous bolus). At higher doses, VCR has shown a significant neurotoxic effect and inter-patient variability in few clinical interventions.




## III. PHARMACOLOGICAL ACTION

The single dose intravenous PK profile of VCR consists of drug concentration vs time graph has shown bi or tri-exponential kinetics with a very fast initial distribution followed by a longer elimination half-life. The clinical PK data of VCR showed long range parameters in human subjects such as half-life from 155 to 1500 min, volume of distribution (Vd) 57–420 L/m2 and clearance value is 82–482 ml/min/m2 Hence, VCR has a large volume of distribution indicating a wide distribution in the body and extensive binding to tissues. PK of VCR revealed its affinity towards normal cells and less binding capacity with tumour tissues, which limits antitumour efficacy of the drug in vivo. It quickly absorbed by liver cells and reduces its delivery to cancer cells using a saturation process. Based on the kinetic data, hepatocytes uptake amount might be up to 500 times more than other tissues. Evidently, it accumulates heavily in the eye, and fatty tissues except the brain. Additionally, VCR has low affinity for the central nervous system compared to plasma. These pharmacological properties limit clinical benefit of VCR by limiting plasma and cancer tissue drug exposure. VCR mostly metabolized through cytochrome CYP3A4 and CYP3A5 enzymes of liver shown in. Also, co-administration of another active ingredient increases or reduces the metabolism of VCR. The phenobarbital functions as CYP3A inducer which leads to rapid clearance of VCR from systemic circulation. The clinical studies have shown that CYP3A5 exhibited an important role in P450 derived elimination of VCR and cytochrome genetic factors variability in patients. The high-pressure liquid chromatography analysis revealed that VCR was mostly excreted out from plasma to bile and urine.

## IV. MEDICINAL 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 R-CVP, Hodgkin's lymphoma as part of MOPP, COPP, BEACOPP, or the less popular Stanford V chemotherapy regimen in acute lymphoblastic leukemia (ALL), and in treatment for nephroblastoma as well as the chemotherapy regimen VDC-IE for Ewing's Sarcoma. It is also used to induce remission in ALL with dexamethasone and L-asparaginase, and in combination with prednisone to treat childhood leukemia. Vincristine is occasionally used as an immunosuppressant, for example, in treating thrombotic thrombocytopenic purpura (TTP) or chronic idiopathic thrombocytopenic purpura (ITP).

## V. SIDE EFFECTS

The main side effects of vincristine are chemotherapy-induced peripheral neuropathy,

hyponatremia, constipation, and hair loss. Vincristine-induced neuropathy is the main dose-limiting side effect. Chemotherapy-induced peripheral neuropathy can be severe, and may be a reason to reduce or avoid using vincristine. The symptoms are progressive and enduring tingling numbness, pain and hypersensitivity to cold, beginning in the hands and feet and sometimes affecting the arms and legs. 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) should avoid vincristine. A 2021 study has suggested that anakinra can reduce the neuropathy. Accidental injection of vinca alkaloids into the spinal canal (intrathecal administration) is highly dangerous, with a mortality rate approaching 100 percent. The medical literature documents cases of ascending paralysis due to massive encephalopathy and spinal nerve demyelination, accompanied by intractable pain, almost uniformly leading to death. Several patients have survived after aggressive and immediate intervention. Rescue treatments consist of washout of the cerebrospinal fluid and administration of protective medications. Children may do better following this injury. One child, who was aggressively treated at the time of the injection, recovered almost completely with only mild neurological deficits. A significant series of inadvertent intrathecal vincristine administration occurred in China in 2007 when batches of cytarabine and methotrexate (both often used intrathecally) manufactured by the company Shanghai Hualian were found to be contaminated with vincristine. The overuse of vincristine may also lead to drug resistance by overexpression of the p-glycoprotein pump (Pgp). There is an attempt to overcome resistance by the addition of derivatives and substituents to the vincristine molecule.

## VI. TREATMENT OF CANCER

vincristine is mostly used in combination with other anticancer drugs and novel combinations are still being developed.

development of vincristine combination therapy and brings concise evidence for the importance of vincristine in the treatment of blood cancer as well as in the treatment of other malignancies. Here, we summarize respective active clinical trials and briefly report on the mechanism of anticancer action of vincristine and the drugs used in combination with this compound.

vincristine has commonly been combined with methotrexate (Trexall®, Otrexup®, or Rasuvo®, originally developed by Bound Brook researchers), which is a selective inhibitor of the dihydrofolate reductase, an enzyme vital for the thymine nucleotide synthesis. Although the vincristine/methotrexate combination has been tested and used in clinics since the 1960s, its benefits are still discussed. Initial trials evaluated the combination of these two drugs with cyclophosphamide and 5-fluorouracil, which also blocks the synthesis of thymidine. The trials presented positive outcomes in various solid tumors, however, in one of the first studies published on this topic, only a half of the involved patients responded objectively to the treatment and almost all patients were affected by the toxicity of the drug combination.

## VII. FUTURE USES

Nanoparticle delivery
Vincristine can be delivered to cancer cells using nanoparticles, which can reduce side effects and improve targeting.

Monoclonal antibody combinations
Vincristine can be combined with monoclonal antibodies that bind to cancer cell surface receptors.

Targeted therapies
Research is ongoing to develop antibodies that are specific to cancer cells

Future perspective VCR nanofomulation
Based on clinical studies, VCR nanocarriers present huge opportunities as important therapeutic in treatment of various type of cancers. Furthermore, nanocarriers have revealed applications in in vivo system. Nanocarriers offers organ-specific drug delivery that ultimately increase range of theranostic use in future. The nanotechnology mediated cancer therapy results in tumour targeted delivery reducing non-specific distribution of chemotherapeutics and would potentiate and reverse acquired multidrug resistance. Targeted nanocarriers will be used to deliver VCR with immunostimulants in cancer therapy in course to target the main cancer cell communication channels, prevent immune evasion, and counteract chemo resistance mechanisms. For

example, it has been reported that nano-encapsulated cur cumin can be used in conjunction with VCR as a chemo sensitizing agent. In other perspective currently the cutting-edge nanotechnology will be used to treat the vector borne cancer ailment. According to published report, the virus hepatitis B/C and human papilloma virus contribute nearly 12% incidence rate in tumour formation. Therefore, VCR nanocarriers will play a major role in the treatment of virus-related tumours in the future. The decades of immunological studies and relation with nanocarriers revealed their effects and application in immune-cancer therapy and this knowledge will aid in reduction of cancer patient mortality and suffering. Despite the necessity for extensive study, finding the biomarkers for identifying individuals who would benefit from chemoimmunotherapy is crucial. Additionally, the mechanism of immuno-chemo therapy against supportive tumour stroma is unclear, particularly in individuals with advanced disease. Therefore, creating potent VCR nanocarriers is crucial to battling the illness. With the development of targeted delivery medications with precise RNA-based gene sequence com plexes and theranostics treatment of cancer will be easier in the future. The target specific nanocarriers could also be combined with extremely intricate organelle molecular imaging compounds to advance examination and diagnostics in early cancer encounters, particulate tracking instantly, as well as imaging and monitoring the course of therapy.

## VIII. CONCLUSION

Vincristine is a fundamental chemotherapeutic agent.It is used for the treatment of various types of cancers. vincristine reduces the tissue affinity in low cancer cells. ongoing research provides vincristine mechanism of action and clinical uses and also this research gives the information about treatment of chemotherapy and cancer prevention.

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