“The Pain Inducing, Cancer Remedy”: The Occurrence, Bioactivity, Biosynthesis, and Synthesis of Vincristine

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Introduction

Vincristine is an anti-neoplastic drug found in the Madagascar periwinkle (Catharanthus roseus). It is clinically used to treat a range of cancers including various lymphomas and sarcomas, advanced testicular cancer, breast cancer and acute leukemia. Vincristine belongs to a group of bisindole alkaloids derived from tryptophan.

Figure 1. Vincristine, used to treat various types of cancer and can be found in the Madagascar periwinkle.

I. Occurrence

Vincristine is found in Catharanthus roseus, more commonly known as the Madagascar periwinkle. This plant was formerly named Vinca roseus. The genus Catharanthus has eight species, seven of which are endemic to the island of Madagascar and the eighth is found in the subcontinent of India. In the wild, the Catharanthus roseus is an endangered plant due to its habitat destruction. However, it is widely cultivated and globally grown in tropical and subtropical areas.

Figure 2. Catharanthus roseus. source (http://www.biologie.uni-regensburg.de/Botanik/Schoenfelder/kanaren/images/Catharanthus_roseeus.jpg)

Vincristine was approved by the Food and Drug Administration (FDA) in 1984. It is available in the trade under the names Oncovin, Vincasar, and Vincex. This drug was previously known as leurocristine (LCR). The derivatives of the vinca alkaloids include vincristine, vinblastine, vindesine, and vinopocetine.

II. Biological Activity

Vincristine disrupts the formation of microtubules cells, which inhibits the replication of cancer cells. It is generally used as a chemotherapy drug for cancer patients to slow the growth of cancer cells. Vincristine sulfate is widely used to treat leukemia, malignant lymphomas, neuroblastoma, Hodgkin’s disease, Wilm’s tumor, and many other cancers.

Figure 3. Vial of Vincristine. Source (http://www.vghks.gov.tw/ph/%B3%B%A4%E8%B6%B0/drug/vincristine.files/image04.jpg)

Vincristine can only be administered intravenously and if introduced into the spinal cord fluid, it ensures almost absolute death. Patients experience paresthesias because vincristine causes damage to small nerve fibers carrying the sensations of pain and temperature. Another side affect would be a disturbance of nerve fibers that help muscles around the colon that move stool, which means that the patient will experience constipation. Toxic effects may include numbness, pain, tingling, headaches, rashes, a change in blood pressure, dizziness, nausea, vomiting, hearing problems, and hair loss. Effects are more common to those with poor liver function.

Short-term pretreatment with vincristine expresses impressive protective effects in cultured adult mouse myocytes subjected to acute oxidative stress. However, it can damage the patient’s bone marrow or because of its neurotoxicological effects, the amount administered is severely limited. The organism expresses thermo allodyna and mechanical hypersensitivity after taking vincristine. Vincristine expresses unfavourable side effects, but is very efficient in treating various types of cancers. Vinca alkaloids inhibit microtubule formation by binding to tubulin. All four clinically available vinca alkaloids cause neuropathy, but vincristine has the lowest risk for peripheral neuropathy. Similarly, vinblastine has the highest risk of peripheral neuropathy and the only difference N-methyl group rather than N-formyl on the vindoline fragment.
can be an oxidized product from vinblastine. Vinca alkaloids have various beneficial properties besides being anti-mitotic and anti-microtubule drugs. Derivatives of vinca alkaloids have shown to be immunosuppressive drugs and nootropic drugs.

III. Biosynthesis

Vincristine belongs in a group of alkaloids that derive from tryptophan. The structure of vincristine is derived by coupling of two alkaloids, catharanthine and vindoline. The biosynthesis of vincristine is summarized in Figure 4. First, catharanthine (1) is oxidised by a peroxidase catalyst (2), which forms a peroxide which acts as a leaving group. When the peroxide leaves, the carbon-carbon bond is broken and the intermediate electrophilic ion (3) is attacked by the nucleophilic vindoline (4). The molecule is then reduced in the dihydropyridinium ring by NADH-dependent 1,4-addition, giving the substrate for hydroxylation (7). Finally, reduction by NADH yields vincristine.

![Figure 4. Biosynthesis of Vincristine.](image)

IV. Synthesis

Like the biosynthesis, the synthesis of vincristine is composed of catharanthine and vindoline. Catharanthine is catalyzed by m-chloroperbenzoic acid which adds a negatively charged oxygen to form catharanthine N-oxide (9). When the carbon-carbon bond is broken by the trifluoroacetic anhydride, the intermediate electrophilic ion (10) is attacked by the nucleophilic vindoline (11). The substrate is then reduced in the dihydropryridinium ring and oxidized by ferric chloride and oxygen (14). Finally, vincristine is formed by reduction by sodium borohydride.

There are other methods for the synthesis of vincristine. The synthesis of (+)-vincristine has been accomplished through a stereoselective coupling of demethylvindoline and the eleven-membered carboxymethoxyverbanamine precursor. The oxidation of 17-hydroxy-11-methoxytabersonine, followed by regioselective acetylation with mixed anhydride method yielded demethylvindoline. Fukuyama’s first de novo syntheses of these alkaloids was published in 2002 and 2004, but researchers continue to find new and efficient methods that allow for the assembly of key substructures of vincristine.

![Figure 5. Synthesis of Vincristine.](image)
Conclusion

Vincristine is a very interesting and useful drug. Derived from catharanthine and vindoline through the alkaloid pathway, it is used to treat various cancers by disrupting the formation of microtubules cells, which inhibits the replication of cancer cells. This drug can only be introduced intravenously and causes slight nerve damage. Vinca alkaloids possess beneficial properties such as slow cancer cell growth, yet they have slight toxic effects and occasionally cause the patient to be in pain. Since vincristine expresses the lowest risk of peripheral neuropathy out of the four vinca alkaloids, the positive effects outweigh the negative. Vincristine is a useful drug used to treat various lymphomas and sarcomas, advanced testicular cancer, breast cancer, acute leukemia, neuroblastoma, and other types of cancers. The development of an easy synthesis for vincristine is important and researchers continue to find new and efficient for the synthesis of vincristine.

References


