

Role of vinca alkaloids and their derivatives in cancer therapy

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Abstract

Vinca alkaloids and its derivatives like Vincristine, Vinblastine etc. isolated from *Catharanthus roseus* plants are widely used in the treatment of various types of cancers. Mode of action of Vinca alkaloids (vinblastine, vincristine, vinorelbine) is microtubule-stabilizing agents (MTAs) i.e., arrest the cell cycle via disrupting microtubule dynamics. Vincristine major side effect is neurotoxicity. However, Vincristine induce neuropathy in mice or rat, used as animal model to study effect of drugs or plants by various authors also reported in review literature. Vinca alkaloids and its derivatives were widely used drugs in combination regimens with cyclophosphamide, doxorubicin, procarbazine, Methotrexate and dacarbazine etc. in various types of cancer. In this review, we also discussed major structure modifications position of chemically synthesized vincristine and vinblastine derivatives required for potential anticancer activities. Anticancer mechanism and some major patents on vinca alkaloids derivatives also reported in this review article. The study of Vinca alkaloids and its derivatives a class of an antimitotic compounds, found essential role in anticancer therapies.

Keywords: Cancer; Vinca Alkaloids; Microtubule-stabilizing agents (MTAs); Vincristine (VCR) induce neuropathy

1. Introduction

According to IARC (International Agency for Research on Cancer) approx. 13% of cancer cases diagnosed in 2018 and over 10 million deaths in 2020 is due to cancer [1]. Worldwide record of deaths due to cancer is accounting from 9.6 million in 2018 to over 10 million in 2020 and increasing. Most common deaths due to breast cancer (2.26 M.), lung (2.21 M.), prostate (1.41M.). Every year, approx. 0.4 million children diagnose with cancer [1]. Consuming of tobacco, poor diet, air pollution, absence of physical exercise is major cause of cancer [1].

A class of organic compounds obtained from plants, which contains hydrogen, oxygen, nitrogen, carbon groups and has the alkaline properties they are known as the alkaloids [2, 3]. The group of alkaloid plants used in the treatment of cancer are the vinca alkaloids. Vinca alkaloids are an extract from *Catharanthus roseus* (basionym *Vinca rosea*) commonly called pink periwinkle plant or vinca plants (Figure 1) [2, 4-7]. It is a class of drug, which is used in treatment of various types of cancer such as lung cancer [2]. It showed the hypoglycemic and cytotoxic effects on the body [3]. It is a class of anti-mitotic agents and anti-microtubule alkaloids; it blocks the beta-tubulin polymerization in dividing cell [7]. Which helps in treating the cancer growing cells. Types of vinca alkaloids some of them are Vinblastine (VBL), Vincristine (VCR), Vinorelbine (VRL), Vindesine (VDS), Vinflunine, etc. are majorly used in clinical treatments (Figure 2) [2,3, 7-8]

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Vinca alkaloids has existence of indole, pyrrole and carbazole structure and play a major role in the development of new anticancer agents [4-6]. In most of the class of cancer treatment, drug vinca alkaloids are the best for the cancer therapies and these are used as second line treatment for cell carcinoma [2, 3]. It was first discovered in 1950 by two Canadian scientists, Robert noble and Charles beer. They are the cell specific cytotoxic drugs which act on the tubulin, which forms microtubules during cell division, thus it helps the carcinogenic cell to divide further. Some of the vinca alkaloids (Vindesine) are produced synthetically for the treatment and also as immunosuppressive drugs [7, 8]. Compounds are vinblastine ($C_{46}H_{58}N_4O_9$), vincristine ($C_{46}H_{56}N_4O_{10}$), Vinorelbine ($C_{45}H_{54}N_4O_8$) etc. The discovery of vinca alkaloids as the anticancer effect was accidental research as when they found that the extract has the oral hypoglycaemic effect on body, they noticed that the sever decrease in WBCs, granulocytopenia and bone marrow destruction rather than anti diabetic action in rats [2,3]. After that more researches shows the possibilities of vinca alkaloids as anticancer drugs. In 1963, Drug like Vincristine sulfate (oncovin) successfully approved as chemotherapy regimens by FDA (Food and Drug Administration) [7,8].



Figure 1 Catharanthus roseus plant

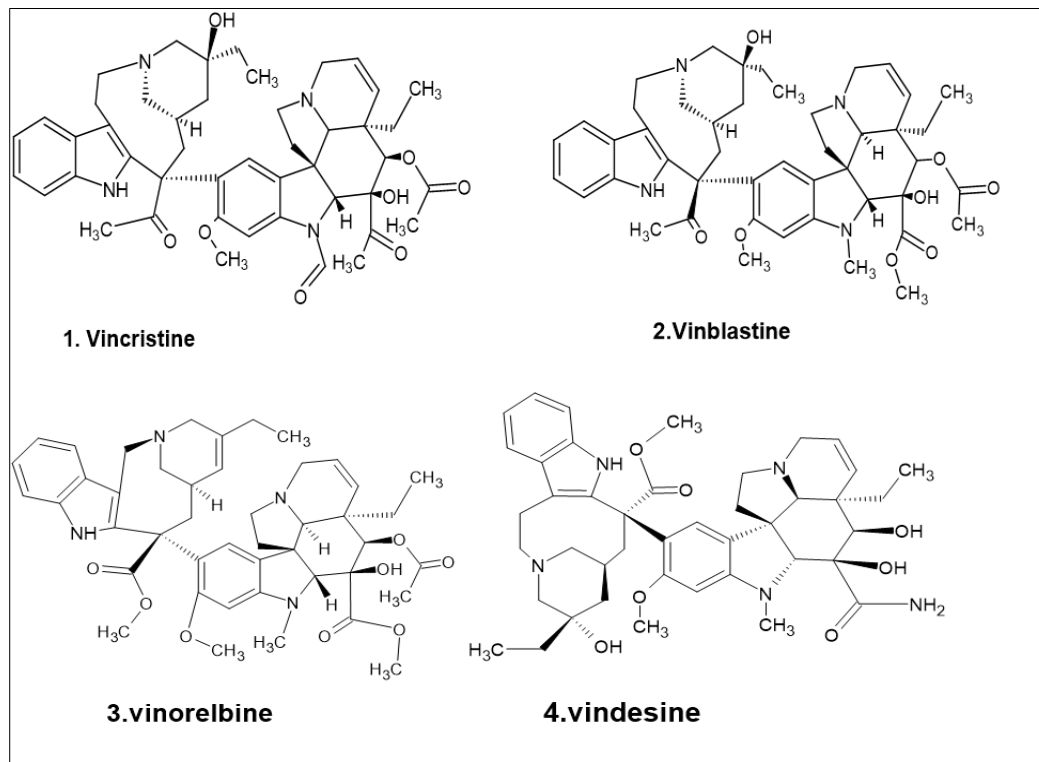


Figure 2 Structure of Vincristine (1), Vinblastine (2), Vinorelbine (VRL, 3), Vindesine (VDS, 4)

Newly synthesis synthetic vinca alkaloid Vinflunine, which may use as the second line treatment for metastatic transitional cell carcinoma of the urothelium, is also approved by the EMA (European Medicines Agency) [2]. Cost of

production and taken by intravenous injection route (I.V.) is major hurdle for the frequent use in the Vincristine and its derivatives in chemotherapy [4-6]. We also given some major patents on vinca alkaloids and its derivatives useful of cancer therapy in Table-1. Indole, pyrrole or tetrahydrocarbazole structures are present in vinca alkaloids and plays an important role in development of new anticancer agents [6, 10,11].

Table 1 Some major patents on vinca alkaloids and its derivatives used in cancer therapy

S.No.	Patent No.	Title	Inventor	Year / [ref.]
1.	US4,210,584A	VINDESINE SYNTHESIS	Gloria C. Paschal, Gerald L. Thompson.	Jul.1, 1980 / [12]
2.	US4,375,432A	METHOD OF PREPARING VINCRISTINE	Robert A. Conrad	Mar.1,1983 / [13]
3.	US4910138A	USE OF AN ORGAN CULTURE OF CATHARANTHUS ROSEUS TO PRODUCE VINCRISTINE AND VINBLASTINE	Yoshiharu Miura, Kazumasa Hirata.	Mar.20,1990/ [14]
4.	US5047528A	PROCESS OF SYNTHESIS OF VINBLASTINE AND VINCRISTINE	James P. Kutney, Lewis S. L. Choi, Jun Nakano, Michael McHugh,	Sep.10,1991/ [15]
5.	US 6,365,735 B1	VINCA-ALKALOID DERIVATIVES AND PREPARATION METHOD	Patrice Rool	Apr.2,2002 / [16]
6.	US 7,235,564 B2	VINORELBINE DERIVATIVES	Ian L. Scott, Jeffrey M. Ralph, Matthew E. Voss	Jun.26,2007 / [17]

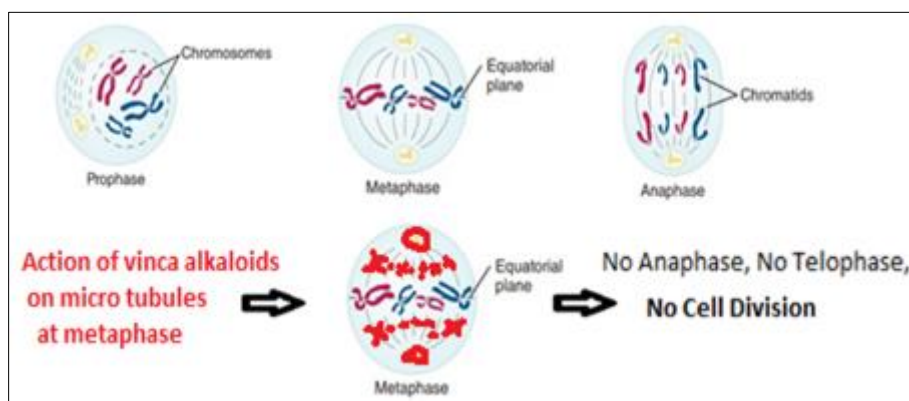


Figure 3 Anticancer mechanism of Vinca Alkaloids

2. Mechanism of action of vinca alkaloids

Vinca alkaloids act directly on the mitotic phase of cell cycle and stops the further division of the cell division (Figure 3). It binds with the tubulins of spindle fibres and disrupters the micro tubules formation which arrest the cell into the metaphase(Figure 3)[2-3]. Vinca alkaloids depolymerize the micro tubules and destabilized the mitotic spindles which resulting in cell death [6, 7, 8]. Microtubule-targeted antimetotic drugs are classified into two main groups like microtubule-destabilizing agents and microtubule-stabilizing agents. Vinca alkaloids (vinblastine, vincristine, vinorelbine) are examples of microtubule-destabilizing agents [6, 9].

3. Structure modification in vinca alkaloids

Vincristine (1) and vinblastine (2) have two monomer alkaloid parts: catharanthine (5) and vindoline (6) (Figure 4). The difference between vinblastine (2) and vincristine (2) is that the former has a methyl while the latter has a formyl

group on the indole nitrogen of the vindoline skeleton and both differ in both the clinical activity and toxicity profiles [18]. Major structural modification in both Vinca alkaloids were carried at N-3, 4, 6, 7 and 10th position. However modification at N-1, 6, 7 position lead to loss of anticancer activity of the Vinca alkaloids [18-19]. The conversion of carboxylic acid ester at position 3 to amide followed by deacetylation at C- 4 in the lower vindoline portion of vinblastine gave Vindesine (7) is approved for use in Europe for treatment of melanoma cancer [20]. F. Orosz and co-workers synthesized Spiro-oxazolidinedione substituted derivatives of vincristine and vinblastine from the reaction of the 4-deacetoxy vinblastine and 4-deacetoxy vincristine with isocyanates gives KAR-2 [3'-(β-chloroethyl)-2',4'-dioxo-3,5'-spiro-oxazolidino-4-deacetoxy-vinblastine (8) and KAR-3[3'-(β-chloro ethyl)-2',4'-dioxo-3,5'-spiro-oxazolidino-4-deacetoxy-vincristine] (9) found good cytotoxicity(IC₅₀) values of 0.31 μM ± 0.06 and 0.31 μM ± 0.05 compared to vincristine (IC₅₀ = 0.005 μM ±0.001) and vinblastine (IC₅₀ = 0.013 μM ±0.001) respectively against neuroblastoma cell line (Figure 4) [21-22]. Hiroaki Gotoh et al. reported two compounds 10'-fluorovincristine 11 (IC₅₀ = 0.8 nM and 1.5 nM) and 10'-fluorovinblastine 12 (IC₅₀ = 0.7 nM and 0.8 nM) showed better cytotoxicity compare to vincristine (IC₅₀ = 6.0 nM and IC₅₀ = 7 nM) and vinblastine (IC₅₀ = 6.0 nM and IC₅₀ = 6.8 nM) against L1210 and HCT116 cell line (Figure 4) [22]. Deacetylation of C-4 position in vinblastine gave 4-desacetylvinblastine (13), also showed better *in vitro* anticancer profile against L1210 (IC₅₀ = 5.8 nM) and HCT116 (IC₅₀ = 5.8 nM) cell line respectively. Desacetoxylation at C4 position in lower vindoline portion of vinblastine give compound 14 showed loss of *in vitro* anticancer activity against L1210 (IC₅₀= 60 nM) and HCT116 (IC₅₀ = 60 nM) cell line respectively (Figure 4). Any other substituent at C-4 position in vinblastine lead to loss of anticancer activity [23-24].

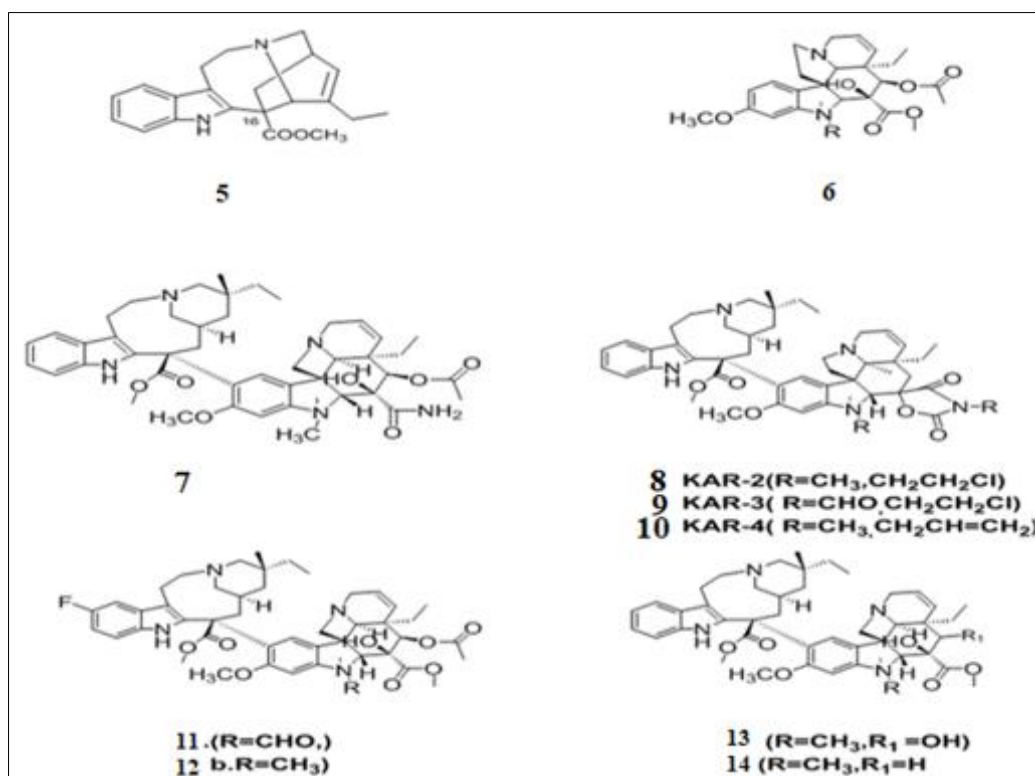


Figure 4 Major structure modifications in Vinca Alkaloids in catharanthine (5) and vindoline (6)

4. Medicinal uses

A source of natural products (Madagascan periwinkle) produces chemotherapy agents (vincristine, vinblastine) which are driven from vinca alkaloids, vindoline and catharanthine [3].

Clinical efficacy of these vinca alkaloids for anticancer properties is broad spectrum by single use or in combination [2, 7, 8, 25]. Vinca alkaloids shows their effect on both malignant and non-malignant cells [3].

Vinca alkaloids are used for the treatment of various types of cancer therapy, they are given in combined form with other drugs as they did not show any side effect or any cross resistance to the drug molecules [3, 6-8]. Vinblastine has widely use in the treatment of various types of cancer and use as the major medical treatment in the therapy of testicular

carcinoma [7, 8, 9, 10]. Vincristine is one of the drugs in PCV (Procarbazine, Carmustine, and Vincristine) chemotherapy used for the treatment of brain tumor [4-6].

VBL can also be used as in the treatment of tumor in germ cells and for the breast cancer treatment. Some of the side effect of vinblastine, which shows toxicity to white blood cells, vomiting, dyspnea, nausea, tumor pain, wheezing and fever [2-8]. Vinorelbine shows similar effect as the vinblastine, VRL shows the greater antitumor activity among the patient suffering from breast cancer and also shows effect on bone cells tumor, osteosarcoma. Vinorelbine affect the lipid bilayer membrane and decreases the stability [2, 3].

Vincristine can be useful in the treating the acute leukemia, neuroblastoma, wilm's tumor and other lymphomas [7, 8]. It has some common side effect peripheral neuropathy, suppression of bone marrow activity, constipation, nausea and vomiting [5-8].

Vindesine, a vinca alkaloid that has broad spectrum antitumor activity in-vitro also less neurotoxicity. VDS administered with methotrexate in L1210 leukemia cells which result in 200% increment in the life span of mice, whereas vindesine administered with Epirubicin didn't affect the efficacy of the drug [9]. Vindesine has antineoplastic activity reported in acute lymphocytic leukemia, malignant melanoma, breast, esophageal and colorectal carcinomas [3]. Vinflunine, the first fluorinated microtubule inhibitor that belongs to the vinca alkaloids. It used as the first line advanced breast cancer treatment [3].

4.1. Toxicity

Vinca alkaloids has toxicity profiles in different extensive properties but all the vinca alkaloids has characteristic toxic effect of peripheral neurotoxicity [7, 8, 25]. VBL and VRL shows less frequency towards the severity of neurotoxicity then VCR [3].

VCR shows rare conditions of hematologic toxicity and sever cases with myelosuppression condition. Vinorelbine have a heavy risk of adverse drug reaction to haematological and non-haematological in patients [3]. VBL, VDS, VRL they show main dose limiting toxicity in neutropenia. Pregnant women should avoid the use of such vinca alkaloid drugs and should not take any vaccine during the treatment with these drugs. [2,3]. Vincristine induce neuropathy however, it also study to use an animal model for induction of neuropathy in mice or rat by various authors [26-29].

5. Conclusion

Vinca alkaloids is the second widely used anticancer drugs for the treatment of cancer therapies. They showed best anticancer effect when its gives to combination drug regimens such as cyclophosphamide, doxorubicin, procarbazine, Methotrexate and dacarbazine in treatment of various types of cancer. They do not show any cross-resistance. Vinca alkaloids such as VCR, VBL, VRL, VDS are synthetically produced and has proven the best drugs for the treatment of cancer.

Compliance with ethical standards

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Disclosure of conflict of interest

Have no conflict of interests to declare by authors.

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