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Cancer therapy with Vinca Alkaloids

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Abstract

Vinca alkaloids are well known antimitotic or antimicrotubule agents, originally derived from the medicinal plant *Catharanthus roseus* (Apocynacea) and other Vinca plants. They have a wide spectrum of anticancer activity both *in vitro* and *in vivo*. The most important members of this family are vinblastine and vincristine (naturally occurring), and their semisynthetic derivatives viz., vindesine, vinorelbine, vinflunine, which were approved by FDA as drugs in cancer therapy. They are used alone or in combination with other anticancer agents for the treatment of a variety of cancers including leukemias, lymphomas, advanced testicular cancer, breast and lung cancer and kaposi's sarcoma. In this article, some cancer related relevant information of Vinca alkaloids are discussed.

Keywords: Antimitotic, *Catharanthus roseus*, *chemotherapy,* Vinca alkaloids.

Introduction

Natural products have produced enormous variety of compounds, which have been used for design of novel therapeutic agents against cancer (Cragg and Newman, 2001, Bhanot et al., 2011). Since the 1940s, out of the total of 175 small molecules discovered and approved as anticancer drug, 49% (85/175) are being either natural products or their derivatives (Newman and Cragg, 2016). The structural diversity as well as the presence of large number of chiral centres of these compounds provides a basis for their use in further drug development.

Currently, drug discovery from plants has relied mainly on bioactivity screening methods and isolation of bioactive molecule (Brusotti et al., 2014). These compounds often serve as "lead" molecules which can further be optimized for better activity, reduced toxicity, or improved pharmacokinetics to maximize their therapeutic potential. The major class of secondary metabolites, such as alkaloids, terpenoids, steroids, flavonoids, saponins etc., with unique pharmacophore, have been isolated from plant sources and are considered important "leads" for the treatment of a variety of cancerous diseases (Gopalakrishnan et al., 2014). For example, phytochemicals like vinblastine, vincristine, camptothecin, podophyllotoxin, paclitaxel, homoharringtonine and some of their derivatives are very well known clinically approved anticancer drugs

used either by alone or in combination with other chemotherapeutic agents (Cragg and Newman, 2005, Sisodiya, 2013).

Vinca Alkaloids

Alkaloids are an important class of phytochemicals having a varied spectrum of biological activities. They are naturally occurring nitrogenous heterocyclic bases, and many of them are the main active constituents of various medicinal plants (Kaur and Arora, 2015). They have potent anticancer activity against several cancerous diseases (Mohan et al., 2012). In fact, the first significant anticancer alkaloid, viz., vinblastine and vincristine isolated from aerial parts (mainly stem and leaf) of Madagascar periwinkle plant, *Catharanthus roseus* G. Don (family: Apocynacea) introduced new era in anticancer drug discovery (Johnson et al., 1960).

Ethnomedical uses

Catharanthus roseus G. Don (Apocynacea), syn. *Vinca rosea* Linn. (Figure 1) is an ever blooming sub-shrub, widely cultivated as an ornamental in gardens throughout the world.

Fig. 1. *Catharanthus roseus* G. Don (Apocynacea).

This plant is regarded as a rich source of pharmaceutically important terpenoid indole alkaloids (Vinca alkaloids), having a hypoglycemic as well as cytotoxic effects. Traditionally, the plant has been used to treat diabetes, high blood pressure and have been used as disinfectants (Gueritte and Fahy, 2005). Again, it was noted that extracts reduced white blood cell counts and caused bone marrow depression in rats, and subsequently they were found to be active against lymphocytic leukemia in mice. This led to the isolation of vinblastine and vincristine as the active agents, so their discovery may be indirectly attributed to the observation of an unrelated medicinal use of the source plant (Cragg and Newman, 2005).

Anticancer effects

The Vinca alkaloids have played a vital role as a source of effective anticancer agents (Noble, 1990). The most important clinically used Vinca alkaloids are vinblastine and vincristine along with their semisynthetic analogues viz. vindesine, vinorelbine, vinflunine (Figure 2).

Different Vinca alkaloids have their own unique properties as summarized in Table 1 (Bhanot et al., 2011, Almagro et al., 2015).Currently, vinblastine, vincristine, vinorelbine and vindesine have been used in clinical trials, although only vinblastine, vincristine and vinorelbine have been approved for medical treatment in the United States (Moudi et al., 2013). These compounds are primarily used in combination with other cancer chemotherapeutic drugs for the treatment of a variety of cancers, including Hodgkin's disease, lymphocytic leukemia, neuroblastoma, carcinoma of human cervical, breast and lung, soft tissue sarcomas etc (Mohan et al., 2012, Sisodiya, 2013, Archna et al., 2016). Vinflunine, a fluorinated analogue of vinorelbine, has been approved in Europe for the treatment of second-line transitional cell carcinoma of the urothelium tract and first-line advanced breast cancer (Oing et al., 2016).

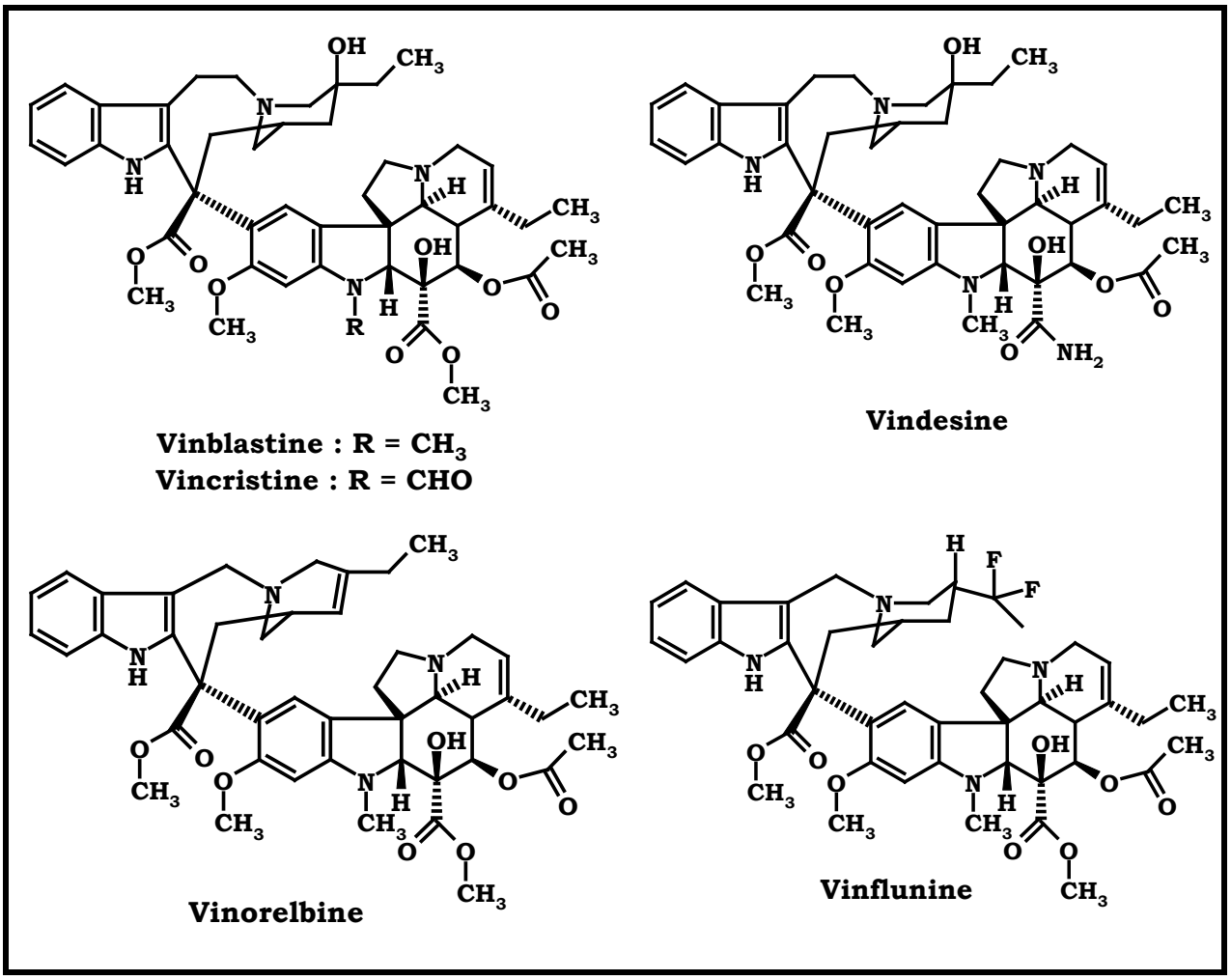

Fig. 2. Structure of clinically used anti-cancer Vinca alkaloids.

Table 1. Anti-cancer Vinca alkaloid analogues in clinical practice.

Generic name [Year introduced]	Source	Activity / Treatment regimens	Side Effect	Stage of Clinical Development
Vinblastine (VBL) [1965]	Natural product	Testicular carcinoma; both Hodgkin disease and non-Hodgkin lymphomas; breast cancer; germ cell tumors.	WBC, nausea, vomiting, constipation, dyspnea, chest or tumor pain, wheezing and fever.	In clinical use; 22 combination trials in progress.
Vincristine (VCR) [1963]	Natural product	Acute leukemia; rhabdomyosarcoma; neuroblastoma; Wilm's tumor; Hodgkin's disease and other lymphomas;	Peripheral neuropathy, suppression of bone marrow activity, constipation, nervous	In clinical use; 108 combination trials in progress.

		several non-malignant hematologic disorders.	system toxicity, nausea and vomiting.	
Vindesine (VDS) [1979]	Natural product derived	Acute lymphocytic leukemia; blast crisis of chronic myeloid leukemia; malignant melanoma, pediatric solid tumors; metastatic renal, breast, esophageal and colorectal carcinomas.	Anemia; blood cell toxicity; fatigue; tingling or pricking sensations in the skin; skin toxicity.	In clinical use; phase III clinical trials in progress.
Vinorelbine (VRL) [1989]	Natural product derived	Breast cancer; osteosarcoma; decreases the stability of lipid bilayer membranes; approved for the initial treatment of patients with advanced lung cancer.	Anemia, constipation, diarrhea, nausea, numbness peripheral neuropathy and inflammation at the injection site, hair loss, allergic reaction.	In clinical use; 29 phase I - III clinical trials in progress (single and combination).
Vinflunine (VFL) [2010]	Natural product derived	Transitional cell carcinoma of the urothelial tract; non-small cell lung cancer; breast carcinoma.	Nausea; vomiting; diarrhea; chest pains; fever.	Phase III.

Overall, Vinca alkaloids are the second-most-used class of cancer drugs and will stay among the original cancer therapies

Mechanism of anticancer activity

Microtubules are essential components of the cytoskeleton and play a crucial role in eukaryotic cellular functions such as intracellular organelle transport, cell migration, cell signalling and mitosis. They are involved in chromosome separation during mitosis and meiosis, and are the major constituents of mitotic spindles, besides they are involved in maintaining cell structure, transportation and many others cell functions (Hadfield et al., 1998, Jordan, 2002). The main mechanisms of Vinca alkaloid 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, leading to programmed cell death or apoptosis (Coderch et al., 2012). However, they can do many other biochemical activities that may or may not be related to their effects on microtubules. They 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.

Conclusion

The ancient medicinal plant *Catharanthus roseus* is an amazing chemical factory, producing more than 130 terpenoid indole alkaloids, out of which Vinca alkaloids are most important for their role in anticancer chemotherapy. Vinblastine and vincristine are the first plant derived anticancer drugs came

into clinical use. Along with these two plant products, some of their semi-synthetic analogues are also used clinically in combination chemotherapy regimens for the treatment of a variety of cancers specially those that are multidrug resistant. These compounds are the second-most-used class of cancer drugs and will stay among the original cancer therapies. Thus, Vinca alkaloids have set a milestone in the 'History of Modern Anticancer Medicine'. A little of its usage in medicine has been established by numerous studies; still more of its hidden properties are yet to be explored to reveal the unknown mysteries which would help the need of the present pharmaceutical world.

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