International Journal of Pharmacognosy and Life Science

E-ISSN: 2707-2835
P-ISSN: 2707-2827
IJPLS 2020; 1(2): 38-43
Received: 23-05-2020
Accepted: 26-06-2020

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Vincristine: Beyond on anticancer treatment

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DOI: https://doi.org/10.33545/27072827.2020.v1.i2a.17

Abstract
Vincristine is a chemotherapeutic agent that is a component of many combination regimens for a variety of malignancies, including several common pediatric tumors.78% of patients with advanced malignant disease were treated with vincristine, an alkaloid derived from *vinca rosea* Linn, 59% of these survived from the beginning of treatment and could be evaluated. Favourable responses were seen in patients with Hodking's disease, reticulum cell sarcoma, lymphosarcoma, carcinoma of the breast, acute leukemia and choriocarcinoma. Toxic include a high incidence of alopecia and neurologic complications. Vincristine treatment is limited by a progressive sensorimotor peripheral neuropathy. Vincristine-induced peripheral neuropathy (VIPN) is particularly challenging to detect and monitor in pediatric patients, in whom the side effect can diminish long term quality of life. Further research is needed to predict, prevent, and treat disease to maximize therapeutic benefit and avoid unnecessary toxicity from vincristine treatment.

Keywords: Vincristine, *Catharanthus rosea* Linn, hodking's disease, lymphosarcoma, vincristine induced peripheral neuropathy

Introduction
Vincristine is originally derived from the periwinkle plant *Catharanthus roseus*. Vincristine act as inhibitors during the metaphase of the cell cycle and by binding to the microtubules inhibit the development of the mitotic spindle [1]. The vinca alkaloids are important for being anticancer drugs like vincristine and vinblastine. The productivity of vinblastine and vincristine is very low in plants (0.001-0.0003%) resulting in their extraordinary high price [2]. The United States Food and Drug Administration (FDA) approved indications of vincristine are acute lymphocytic leukemia, lymphoid blast crisis of chronic myeloid leukemia and Hodgkin and Non-Hodgkin lymphoma [3]. Vincristine also has several off-label uses that include central nervous system (CNS) tumors, Ewing sarcoma, gestational trophoblastic tumors, multiple myeloma, ovarian cancer, primary CNS lymphoma, small cell lung cancer, and advanced thymoma in adult patients [4].
The productivity of vinblastine and vincristine is very low in plants (0.001-0.0003%) resulting in their extraordinary high price. Vinblastine is a dimeric indole alkaloid and is formed by coupling of vindoline and catharanthine catalysed by horseradish peroxidase1. The yield of coupling products, (15' 20'- anhydro vinblastine) was reported very low (0.9%) [5]. Vinblastine is converted into vincristine by the oxidation of its methyl group. Most of the key enzymes of the indole alkaloid biosynthetic pathway have been isolated from seedlings and/or cell suspension cultures of the C. roseus 2 [6]. The cell cultures do not produce dimeric and monomeric indole alkaloids but catharanthine is produced in considerable amounts. Vincristine, vinblastine and vindoline were reported only in shoot cultures and differentiated tissues but not in roots [7]. Recently a stable, high producing and salt tolerant cell lines of *C. roseus* plant has been developed to achieve industrial production of the alkaloids. The major limitation of these drugs in cell cultures is their low yield. Particularly the improvement of catharanthine production in *C. roseus* cell cultures is of great interests for pharmacologists and chemists because catharanthine and vindoline can be coupled to form vinblastine in high yield, and vindoline is abundant in plants [8]. Elicitors can also modulate the production of these alkaloids as reported by Moreno *et al*. Involvement of metabolic engineering for alternative production methods was encouraged and made possible due to low vinblastine and vincristine contents in the plants [9, 10]. Engineering techniques like semi-synthesis, total chemical synthesis or even of chemical [11, 12] or enzymatic coupling 13 of commercial

available catharanthine a vindoline is useful plant.

Fig 1: Vinca [13]

Vincristine is used in combination therapy to treat acute leukemias and lymphomas and constitutes an important component of the regime that has been so successful in treating childhood leukemias. Vinblastine is often used in combination to treat bladder and breast cancers and is an integral part of the curative treatment regime for Hodgkin's disease. Vinorelbine was approved for use in Europe (1991) and the U.S. (1995) for the treatment of non-small-cell lung cancer and vindesine has been approved for the treatment of melanoma [14]. Neurotoxicity (vincristine) or myelosuppression (vinblastine) are the main side effects of administration and neutropenia is the principal dose-limiting toxicity of the vinca alkaloids, but recovery occurs following treatment. However, the major limitation to the continued use of the vinca alkaloids is the emergence of drug resistance derived principally from over expression of phosphoglycoprotein (Pgp), an efflux pump that transports many of the major drugs out of the cell. In fact, vinblastine represents one of the most studied prototypical substrates for Pgp efflux responsible for multidrug resistance (MDR). Thus, in addition to identifying vinblastine and vincristine analogues that may address the current dose-limiting toxicities, the development of a modified vinca alkaloid that is not a substrate for Pgp efflux and is efficacious against MDR tumors would constitute a major advance [15, 16]. Additionally, the emerging evidence that the vinca alkaloids also possess antiangiogenic activity that may contribute to their *in vivo* antitumor activity, especially in combination with other drugs, may provide additional future clinical applications. Due to the pharmaceutical importance and low natural abundance of vinblastine and vincristine, *C. roseus* has become one of the most extensively studied medicinal plants serving as a model for biotechnological studies of plant secondary metabolism. Their biosynthesis involves the participation of at least 35 intermediates, 30 enzymes, 30 biosynthetic and 2 regulatory genes, and 7 intra- and intercellular compartments [9]. Presently, the clinical supplies of 1 and related drugs are derived from natural sources [17]. Fortunately, the doses are so small that the production amounts are manageable even with the trace natural abundance of 1 (0.01%) or 2 (0.0003%) in the source plants. Nonetheless, the effort required even for this limited quantity suggests that an efficient synthetic approach might provide a viable alternative. Even the development of an effective coupling protocol starting with the more abundant naturally occurring (+)-catharanthine [18, 10] and vindoline, vinpocetine, vincamine [19] may supplant the direct use of plant produced vinblastine or vincristine. Interestingly, only C. roseus produces catharanthine and does so with an absolute configuration enantiomer with structurally related alkaloids also found in C. roseus and related alkaloids found in nature. More significantly, an effective synthetic approach would provide access to analogues that incorporate deep-seated structural changes that have not yet been explored [20]. Typically, it has been semi synthetic derivatives of the natural products that have been examined, restricting the structural sites and opportunities to improve on the properties of 1 or 2 [21].

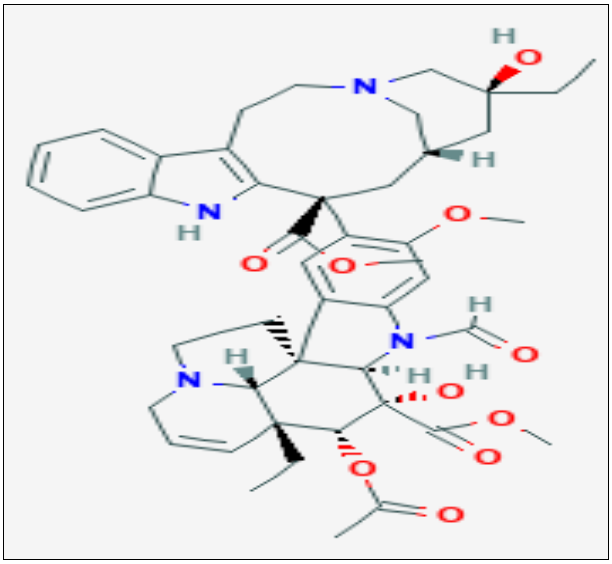

Fig 2: Vincristine

Mechanism of action of vincristine

Vincristine acts by binding to tubulin and inhibiting the formation of microtubules. This inhibition causes mitosis to arrest at metaphase, through the disruption of mitotic spindle formation, especially during the M and S phases [22, 23]. Another mechanism of action of vincristine includes interfering with nucleic acid and protein synthesis by blocking glutamic acid utilization.

Metabolism

Vincristine is rapidly removed from the bloodstream and is tightly bound to tissues, but it poorly penetrates the blood-brain barrier. Vincristine undergoes extensive metabolism in the liver via CYP3A4 [24]. Patients with serum bilirubin levels>3 mg/dl will require dose adjustments; per the manufacturer's label, the dose in such patients should be 50% of the normally administered dose. Vincristine is excreted primarily in the feces.

Pharmacological activity of vincristine on Hodking's disease

Vincristine was found to be useful in the treatment of Hodgkin's disease reticulum cell sarcoma, lymphosarcoma, choriocarcinoma and to a minor degree in the treatment of some mammary tumours. It is generally ineffective in leukemias and in most carcinomas [25, 26]. Toxic effects include depression of erythropoiesis and granulopoiesis, frequent alopecia, occasional gastrointestinal toxicity and occasional neurological complications.

Antiviral effect

The simplex herpes virus (type I) with a cytopathogenicity effect at 0.8 µg/mL.Catharoseumine, a monoterpenoid indole alkaloid, has a unique peroxy bridge, which was identified as a potential inhibitor against falcipain-2 protozoa parasites (causes of malaria), showing an IC50 value of 4.06 µM. Vinblastine and vincristine showed an antiparasitic effect against Trypanosoma that causes trypanosomiasis in humans, inhibiting its mitosis and affecting its cellular shape in a dose-dependent manner [27]. The use of 15 µM of vinblastine and 50 µM of vincristine inhibited cellular division and cytokinesis, and affected cellular morphology, while the effect of 3 µM of vinblastine and 10 µM of vincristine inhibited cytokinesis without affecting cell cycle progression [28, 29].

Antimicrobial activity

Vincristine was tested against microorganisms such as Pseudomonas, Salmonella, Staphylococcus and thus, these extracts show promissory effects as prophylactic agents in the treatment of many diseases. Ramya et al. evaluated the *in vitro* antibacterial activity through the use of crude extracts of *Catharanthus*. The results indicated that leaf extracts showed a higher antibacterial activity than the extracts prepared from other parts of the Catharanthus plant. Thus, the aqueous extracts of leaves, stems, roots and flowers showed low microorganism growth [26, 30] tested leaf extracts of *Catharanthus var. rosea*, which showed an excellent activity against Aspergillus. Stem extracts of var. alba showed a maximum inhibitory activity against Bacillus while the flowers of *Catharanthus var. rosea* showed a higher activity against Bacillus in the methanolic extract [31]. The MIC (Minimal Inhibitory Concentration) against the tested microorganisms was in the range of 100–20 mg/mL. In a different study, foliar acetonic, ethanolic, and chloroformic extracts were tested against pathogenic microorganisms to determine its antimicrobial potential [32]. The ethanolic extract showed the maximum antibacterial activity when compared to the acetonic and chloroformic extracts, in such a way that Staphylococcus was the most susceptible bacteria, followed by Escherichia, Pseudomonas and Streptococcus [33].

Anti-inflammatory activity

Several factors have been suggested as possible predictors for VIN. A study from 2010 aimed to identify predictors for chemotherapy-induced peripheral neuropathy, including vincristine, in 52 patients [34]. It was discovered that the number of chemotherapy cycles was a predictor of VIN, whereas age and co-administration with non-steroidal anti-inflammatory drugs did not correlate with neuropathy incidence and severity. Consistently, Anghelescu *et al*. observed no difference in age between ALL patients with or without neuropathy development [35]. No differences in sex, BMI group, initial leukocyte count, ALL immune phenotype, DNA index, or different genetic translocations were noted. The only significant clinical predictive variable observed was white non-Hispanic race [36].

Genotoxicity

Previous studies have shown that Vinca alkaloids have the potential to induce genotoxic effects in different biological systems. The VCR and VBL have been shown to increase the frequency of micronuclei in experimental animals and in cultured human lymphocytes [37-40]. In addition, they have also been shown to cause chromosomal mutations *in vivo* and in cultured cancer cells [43, 45]. In cultured human lymphocytes, VRB and VCR increased the rate of micronucleus formation. In Drosophila, VCR and VBL induced a significant genotoxic effect as measured using wing somatic mutation and the recombination test [46]. However, some other studies have shown lack of mutagenic effect for Vinca alkaloids *in vivo* and in cultured cells [47-50]. Thus, the genotoxicity of Vinca alkaloids is still controversial. In addition, oxidative DNA damage induced by these compounds has still not been investigated

Ocular toxicity

Vincristine-induced ocular toxicity may be manifested as cranial nerve palsy, optic neuropathy/atrophy, or cortical blindness [51]. Depolarization of neurotubules by vincristine results in neurofibrillary degeneration and impairment of axonal transport [52]. Blindness may occur as the result of optic nerve ischemia, primary toxic axonal injury to the retinal nerve fiber layer, or disruption of microtubule polymerization [53]. The latter was also found to be associated with impairment of axoplasmic flow and loss of neurosynaptic activity in visual cells, resulting in night blindness.

Production of cell culture and tissue culture

The great pharmacological importance of the terpenoid indole alkaloids vincristine and vinblastine, associated to its low content in plants (approximately 0.0005% of dry weight), *in vitro* tissue and cell cultures, will permit the stimulation of intense research regarding the biosynthesis pathways of terpenoid indole alkaloids yet unknown through *in vitro* culture studies under biotic or abiotic elicitation strategies with the objective of increasing the production of C. roseus alkaloids [54, 55].

L-ASP, and dexamethasone against acute lymphoblastic leukemia is enhanced by the BH3-mimetic ABT-737

Several multiagent regimens, including the combination of vincristine, prednisone, and L-ASP, are reported to provide complete response (CR) rates of approximately 40% in multiple-relapse patients [6]. L-ASP, which depletes asparagine and glutamine in leukemic cells [11], is a critical component of therapy for childhood ALL. As a single agent, L-ASP induced complete remissions in 40% to 60% of patients with ALL, and in combination with vincristine and prednisone is associated with an initial remission rate of 95%.12,13 Both *in vitro* and *in vivo* resistance to L-ASP has been associated with poor long-term outcome [56]. In addition, relapsed patients with greater asparagine depletion on day 14 of re-induction were more likely to achieve a second remission in the context of 6-drug therapy [57]. However, expression of asparagine synthetase (AS), which may oppose the action of L-ASP by re-synthesis of asparagine, has varied widely in clinical ALL samples, but a relationship of AS levels to drug resistance has not been reported [58, 59]. ABT-737 is a small molecule that binds to and inhibits the Bcl-2 family anti-apoptotic proteins Bcl-XL, Bcl-2, and Bcl-w. Similar to the BH3-only "sensitizing" protein Bad, ABT-737 does not directly activate Bax or Bak or induce cytochrome c release. Instead, ABT-737 binds to multidomain antiapoptotic Bcl-2 family proteins, preventing them from sequestering proapoptotic BH3-only

proteins.18,19 Overexpression of anti-apoptotic Bcl-2 (Bcl-2 and Bcl-XL) family proteins has been observed in acute myeloid leukemia (AML) [20-22], ALL [23, 24], and other cancers [60]. Bcl-XL overexpression has been reported as an independent predictor of poor event-free survival (EFS) in pediatric ALL [61]. Effective pharmacologic inhibition of the Bcl-2 family of proteins could lower the apoptotic threshold in leukemia cells, resulting in synergy with other chemotherapeutic agents, including drugs commonly used for remission induction in primary and relapsed leukemia, such as vincristine, glucocorticoids, and L-ASP. Using both *in vitro* and *in vivo* models of ALL, we investigated the potential for synergistic activity of ABT-737 in combination with vincristine, L-ASP, and dexamethasone (VXL), drugs commonly used.

Anti-tumour activity

Different percentages of the crude methanolic extracts have been found to show significant anticancer activity against several cell types under *in vitro* conditions and with a high activity against multidrug-resistant tumor types [62]. On the other hand, Ruskin and Aruna showed that the ethanolic extract of vincristine has *in vivo* antitumor activity in the Ehrlich carcinoma tumor model, while the *in vitro* study of the ethanolic extract showed significant antitumor activity

Antileukemic activity

Vincristine is employed to treat lymphocytic acute leukemia (the most frequent malign homeopathy in childhood), of which several chromosomic alterations with prognostic importance are known. Among them there are the translocation [4, 11] and the translocation [9, 22] which are indicators of a bad prognosis, while hyperdiploidy is associated with a good prognosis [63, 64] and it attacks lymphomas including solid tumours in children.

Antioxidant enzymatic activity

An experiment with different concentrations of sodium chloride in two varieties of *Catharanthus (var. alba and rosea)* was carried out [65]. It was found that the enzymatic activity of the superoxide dismutase increased, at levels of 50 mM of sodium chloride, which helps to raise the levels of this enzyme with antioxidant value [66].

Hematologic activity

Overall survival for adult hematologic cancer patients has improved during the past decades due to new treatment options, and more than 80% of children with acute lymphoblastic leukemia (ALL) are now long-term survivors [67]. This therapeutic success, however, comes with the cost of more people experiencing early and late-onset adverse effects, consequently affecting the recovering patient's QOL, which is especially important in children with a long expected lifespan after treatment. Although the intensity of the symptoms may not be extensive, the inconvenience is not correlated, and QOL can be greatly impaired [68]. Given the increasing numbers of cancer survivors, the clinical significance of chemotherapy-induced neuropathy is increasing; consequently, clinical and molecular risk predictors, prevention and treatment options, and measuring methods are urgently warranted [69]. In this paper, we systematically review parameters related to vincristine-induced neurotoxicity in hematologic patients [70].

Conclusion

The vincristine is anticancer drugs that act by binding to intracellular tubulin. In tumour cells, vincristine and vinblastine inhibit the DNA repair and the RNA synthesis mechanisms, blocking the DNA-dependent RNA polymerase [71, 72]. *C. roseus* is an important medicinal plant with several applications in pharmaceutical and industrial products. In the present, vincristine is alkaloids for the treatment of childhood leukemia and Hodgkin lymphoma. Production rate of vincristine in C. roseus is very low, its extraction costly, and too inefficient to be industrialized [73]. The semi-synthesis also faces many obstacles because of the necessary presence of precursors and intermediaries [74]. The great pharmacological importance of the terpenoid indole alkaloids vincristine, associated to its low content in plants (approximately 0.0005% of dry weight), *in vitro* tissue and cell cultures, will permit the stimulation of intense research regarding the biosynthesis pathways of terpenoid indole alkaloids yet unknown through *in vitro* culture studies [75]. Here, I conclude that vincristine has wide variety of pharmacological activity including cancer, further, studies, experiment and research give more pharmacological activity of vincristine.

Acknowledgement

Primarily I would thank God for being able to complete this review with success. Then I would like to thank my co-guide Mrs. Mamta Tiwari and all the author of this review, whose valuable guidance has been helped me to patch his review and make it full proof.

Conflict of interest

None.

Contribution

All authors participated equally.

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