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Drug Delivery Systems and Combination Therapy by Using Vinca Alkaloids

Chun-Ting Lee[1], Yen-Wei Huang[1], Chih-Hui Yang[2] and Keng-Shiang Huang[1,*]

[1]*The School of Chinese Medicine for Post-Baccalaureate, I-Shou University, Kaohsiung, Taiwan;* [2]*Department of Biological Science and Technology, I-Shou University, Kaohsiung, Taiwan*

K.-S. Huang

Abstract: Developing new methods for chemotherapy drug delivery has become a topic of great concern. Vinca alkaloids are among the most widely used chemotherapy reagents for tumor therapy; however, their side effects are particularly problematic for many medical doctors. To reduce the toxicity and enhance the therapeutic efficiency of vinca alkaloids, many researchers have developed strategies such as using liposome-entrapped drugs, chemical- or peptide-modified drugs, polymeric packaging drugs, and chemotherapy drug combinations. This review mainly focuses on the development of a vinca alkaloid drug delivery system and the combination therapy. Five vinca alkaloids (eg, vincristine, vinblastine, vinorelbine, vindesine, and vinflunine) are reviewed.

Keywords: Vinca alkaloids, Drug delivery systems, Combination therapy, Vincristine, Vinblastine, Vinorelbine, Vindesine, Vinflunine, Vinpocetine.

1. INTRODUCTION

Catharanthus roseus (*C. roseus*; Fig. **1**), commonly known as the Madagascar rosy periwinkle or vinca, is a species of herbaceous, perennial tropical plant that grows approximately 1 m tall. Its leaves range from oval to oblong in shape, 2.5 cm to 9 cm long and 1 cm to 3.5 cm broad, and are glossy, green, and hairless, with a pale midrib and a short petiole 1 cm to 1.8 cm long. The flowers vary in color from white to dark pink with a dark red center, and have a basal tube 2.5 cm to 3 cm long and a corolla 2 cm to 5 cm in diameter with 5 petal-like lobes.[1] Vincas have long been cultivated for medicinal purposes. For example, practitioners of traditional Chinese medicine use its extracts to fight against numerous diseases, including diabetes, malaria, hypertension, empyrosis, sores, and Hodgkin's lymphoma.[2] European herbalists created folk remedies with vinca extract for use in conditions that varied from headaches to diabetes. Vincamine, the active compound, and its closely related semi-synthetic derivative widely used as a medicinal agent, ethylapovincaminate or vinpocetine, have vasodilating, blood thinning, hypoglycemic, and memory-enhancing properties.[3, 4] Ayurvedic physicians in India use vinca flowers to brew tea for the external treatment of skin problems such as dermatitis, eczema, and acne.[3, 4] In addition, the juice of the leaves can be applied externally to relieve wasp stings and hyperlipidemia.[5]

Vinca alkaloids have exhibited significant antineoplastic activity against numerous cell types.[3, 4] Five major vinca alkaloids, vincristine, vinblastine, vinorelbine, vindesine, vinflunine, and one of the vincamine, vinpocetine (Fig. **2**), have clinical uses (however, in the United States, only vincristine, vinblastine, and vinorelbine have been approved for clinical use [6]). Researchers have isolated vinblastine in 1958, [7] and later synthesized vincristine, vinorelbine, and vinpocetine, defining them as the vinca alkaloid derivatives.[8, 9] Vinflunine is a new synthetic vinca alkaloid that has been approved in Europe for treating second-line transitional cell urothelium carcinoma.[10] Vinca alkaloids are anticarcinogenic agents that act by binding to intracellular tubulin, which is used in many chemotherapeutic regimens for a wide variety of cancers. The alkaloids inhibit cell division by blocking mitosis, and also inhibit purine and RNA synthesis by killing rapidly dividing cells. Vinca alkaloids are available under the trade names Oncovin® (vincristine), Velban® (vinblastine), and Navelbine® (vinorelbine). Although vinca alkaloids are common drugs used to treat cancers, their side effects cause serious problems. Vinca alkaloids are cytotoxic drugs available by prescription only, and are usually administered through intravenous injection or infusion. Side effects include nausea, vomiting, fatigue, headaches, dizziness, peripheral neuropathy, hoarseness, ataxia, dysphagia, urinary retention, constipation, diarrhea, and bone marrow suppression. In addition, vinca alkaloids are susceptible to multidrug resistance. [11] The risk of side effects and multidrug resistance has limited the development of vinca alkaloids for clinical applications.

To solve these problems, researchers have developed numerous strategies, such as using liposome-entrapped drugs, chemically modified drugs, and polymeric packaging drugs, to reduce the toxicity and enhance the therapeutic efficiency of vinca alkaloids.[10,12-14] Gregoriadis first proposed the concept of liposome-entrapped drugs[12, 15, 16]; currently, various brands, such as DaunoXome®, Myocet®, DOXIL®, Lipo-Dox®, and Marqibo®,[12] are used in clinical applications. Many liposome products, such as SPI-077, CPX-351, MM-398, and MM-302, [12] are still tested in clinical trials. Another strategy for reducing chemotherapy toxicity involves using chemically modified drugs,

*Address correspondence to this author at the School of Chinese Medicine for Post-Baccalaureate, I-Shou University, Kaohsiung, Taiwan;
Tel: +886-988-399-979; Fax: +886-7-6155150;
E-mail: huangks@isu.edu.tw

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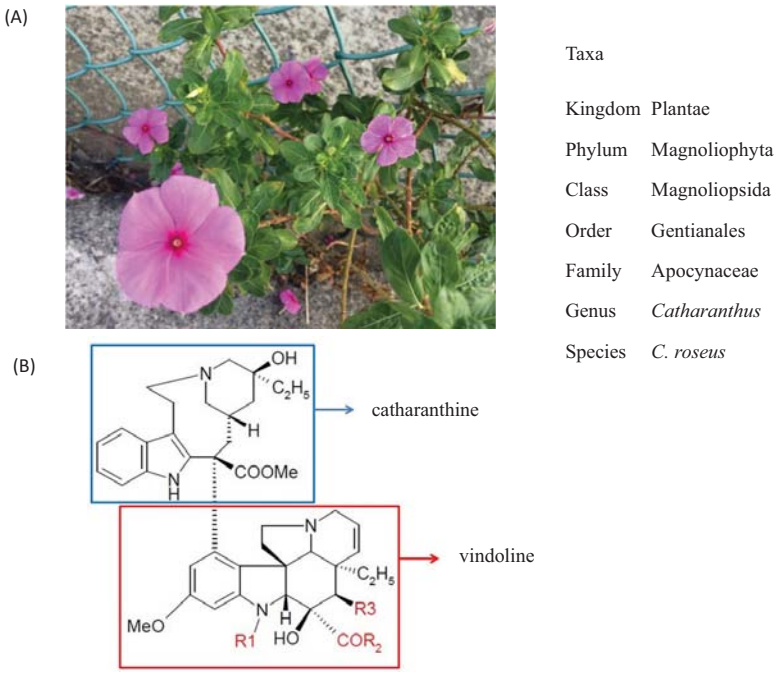

Fig. (1). (**A**) *Catharanthus roseus* (vinca). (**B**) The common chemical core structure of vinca alkaloids, generated by joining 2 alkaloids, catharanthine and vindoline. The substitute group R1 of vinblastin, vindesine, vinorelbine, and vinflunine is methyl, and that of vincristine is formyl. The substitute groups R2 and R3 of vinblastin, vincristine, vinorelbine, and vinflunine are methoxy and acetoxy, whereas those of vindesine are amine and hydroxy. The hydroxylation and alkylation site of catharanthine in vinflunine is modified with ethylidene difluoride.

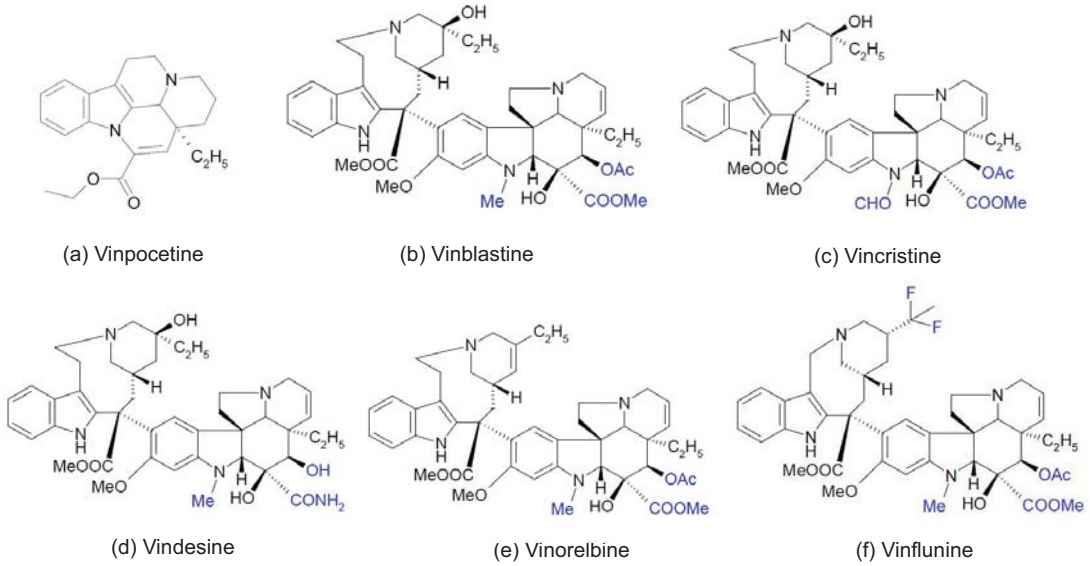

Fig. (2). The chemical structures of alkaloid vincamine and 5 major vinca alkaloids. The vinca alkaloids' variations of substitute groups between them are highlighted in blue to clearly distinguish the differences.

which can target specific proteins that tumors might overexpress, such as folic acid receptors, tyrosine kinases, and tumor neovascular markers. Such as folic acid conjugated drugs, thymidine conjugated drugs, and peptides for tumor neovasculature-targeting conjugated drugs. [17-20] Polymer-entrapped drugs reduce the side effects of chemotherapy. Many studies show that after packing (in which chemotherapy drugs are loaded into poly(lactic-co-glycolic acid)(PLGA), aldehyde poly(ethylene glycol)–poly(lactide), and methoxy poly(ethylene glycol)(PEG)–poly(lactide) (MPEG–PLA) copolymers, the polymer drug delivery systems can enhance the therapeutic effect of cancer chemotherapy.[2, 17, 18, 21, 22] In addition, previous research has indicated that chemotherapy drug combinations are a promising strategy for reducing the side effects of chemotherapy [20].

Vinca alkaloids are one of the most commonly used anticancer drugs. Various topics about vinca alkaloids have been reviewed. [23-33] However, descriptions of the vinca alkaloid delivery system are limited. In this article, we review the developments in drug delivery systems and combination therapies for vinca alkaloids.

2. VINCRISTINE

Vincristine, a natural vinca alkaloid, was first derived from the leaves of C. roseus[34-36] and has been used in tumor therapy since the 1960s as a cell cycle-specific (M-phase) antineoplastic agent.[18, 29, 34-38] The alkaloid can bind to tubulin, causing microtubule depolymerization, metaphase arrest, and apoptosis in cells undergoing mitosis.[18, 34, 35, 39, 40] Vincristine have been used for many years by clinics to treat malignancies including philadelphia chromosome-negative acute lyphoblastic leukemia,[22, 41] B-cell lymphoma,[42, 43] metastatic melanoma,[38] estrogen-receptor-negative breast cancer,[40] glioma,[44, 45] colorectal cancer,[21] non-Hodgkin's lymphoma,[39, 46] Hodgkin's lymphoma, neuroblastoma, rhabdomyosarcoma, multiple myeloma, and Wilms' tumor.[2] However, its applications are restricted by severely neurotoxic side effects.

Determining how to transport vincristine to the specific target without damaging other organs is a critical topic of concern. [47] Table **1** summarizes a few drug delivery systems that have been invented. For example, the blood-brain barrier (BBB) is a natural protectant for the central nervous system; however, it also limits the efficacy of many systemically administered agents.[34] Aboutaleb *et al.* developed a new method that incorporates the freely water-soluble vincristine sulfate into solid lipid nanoparticles with the assistance of dextran sulfate. Their formulation exhibits comparable cytotoxic effects compared to nonpackaged drugs for use against MDA-MB-231 cells.[37] Previous researchers have proved that cetyl palmitate solid lipid nanoparticles is a potential material for vincristine drug delivery to the brain that enhanced the half-life and concentration in plasma and brain tissue by injecting the particles into a rat-tail vein.[37] Folic acid/peptide/PEG PLGA composite particles are another material demonstrating excellent biocompatibility, biodegradability, and mechanical strength that has been used in drug delivery applications for many years. [48-51] Surface modification and the bioconjugate of PLGA composite beads with folic acid, cell-penetrating peptide, and PEG are used to target and enhance drug uptake in MCF-7 cells.[18] In addition, self-assembled dextran sulphate-PLGA hybrid nanoparticles encapsulating vincristine have been utilized to overcome multidrug resistance tumors; this formulation can sustain releasing vincristine. The uptake efficiency of MCF-7/Adr is significantly increased (12.4-fold higher).[52] Multifunctional composite core-shell particles (comprised of a PLGA core, a hydrophilic PEG shell, phosphatidylserine electrostatic complex, and an amphiphilic lipid monolayer on the core surface) have been developed and exhibit sustained-release characteristics in vitro and in vivo, and greater uptake efficiency (12.6-fold) and toxicity (36.5-fold) to MCF-7/Adr cells.[53]

Liposomes, spherical in shape, are composed of phospholipid bilayers that can encapsulate and deliver hydrophilic and lipophilic molecules.[54-58] Because they resemble cell membranes with non-immunogenicity, highly biocompatibility, and safe, liposomes have been widely used in drug delivery systems.[41] Liposomal vincristine (Marqibo®), which has been approved by the US Food and Drug Administration (FDA), has been widely applied in many cancers therapies [22, 39-41, 43, 45, 46]. Table **1** lists the advantages of drug delivery systems, including half-life, uptake, concentration enhancement, and sustained-release characteristics. The size of the composite beads should in nanometer, which can enhance therapeutic efficiency. [59]

3. VINBLASTINE

Vinblastine is a mitotic inhibitor that has been used in the clinical treatment of leukemia, non-Hodgkin's disease, Hodgkin's disease, breast cancers such as breast carcinoma, Wilm's tumor, Ewing's sarcoma, small-cell lung cancer, testicular carcinoma, and germ cell tumors.[6, 72-74] Vinblastine restrains not only the tumor growth, but malignant angiogenesis,[6, 72-76] and can bind specifically to tubulin, inhibiting its polymerization and the subsequent association of microtubules. Side-effects of vinblastine consist of toxicity to white blood cells, nausea, vomiting, constipation, dyspnea, chest or tumor pain, wheezing, fever, and rarely, antidiuretic hormone secretion. [6]

Table **2** summarizes some of the several surface modification, bioconjugate, and drug delivery systems of vinblastine that enhance the therapeutic effects and lower toxicity. For example, thymidine modified vinblastine, forms a thymidine-vinblastine bioconjugate, a bifunctional molecule comprising a microtubule-binding agent and a substrate for a disease-associated kinase. The results showed that fluorescent conjugates of thymidine accumulate in cells in a manner consistent with kinase-mediated trapping, the first account of this type of trapping of cancer therapeutics.[19] In addition, folic acid-vinblastine conjugates have been fabricated to specifically bind to folate receptor overexpressed tumors.[77] Incorporated magnetic nanomaterials in cationic liposomes for tumor vascular targeting have been disclosed. These composite particles can kill vessel cells specifically. [74, 78]

4. VINORELBINE

Vinorelbine is a semi-synthetic vinca alkaloid with a wide antitumor spectrum of activity, especially active in advanced breast cancer and advanced/metastatic non-small-cell lung cancer. Compared with vincristine and vinblastine, vinorelbine is more active and relatively less neurotoxic.[89-92] An injectable form of vinorelbine (Navelbine® IV, Medicament, France) developed by Pierre Fabre is now widely used in clinics. Because vinorelbine is well known to cause venous irritation and phlebitis when directly administered intravenously, [89-92] new drug delivery systems are urgently required. [89-93]

Table **3** outlines a few of the vinorelbine delivery systems. To reduce the severe intravenous formulation side-effects of vinorelbine, a lipid microsphere vehicle has been developed.[89] Takenaga first developed a lipid microsphere in 1996, demonstrating that it can act as a antitumor agent

Table 1. Vincristine delivery systems.

Material	Formula	Size	Treatment	Reference
PLGA	folic acid and peptide conjugated PLGA–PEG bifunctional nanoparticles	~250 nm	MCF-7 cell	[18]
	peptide R7-conjugated PLGA-PEG-folate	-	MCF-7; MCF-7/Adr cell	[59]
	dextran sulphate-PLGA hybrid nanoparticles	~128 nm	MCF-7/Adr cell; rat	[52]
	multifunctional nanoassemblies (PLGA-PEG-PS)	~95 nm	MCF-7/Adr cell	[53]
	PLGA loaded collagen-chitosan complex film	-	-	[60]
	drug-incorporated PLGA microspheres embedded in thermoreversible gelation polymer (drug/PLGA/TGP)	20~49 μm	C6 rat glioma cell; rat	[45]
PEG	folic acid and peptide conjugated PLGA–PEG bifunctional nanoparticles	~250 nm	MCF-7 cell	[18]
	peptide R7-conjugated PLGA-PEG-folate	-	MCF-7; MCF-7/Adr cell	[59]
	multifunctional nanoassemblies (PLGA-PEG-PS)	~95 nm	MCF-7/Adr cell	[53]
	F56 peptide conjugated nanoparticles (F56/PEG-PLA/MPEG-PLA)	~153 nm	CT-26 lung metastasis mice; HU-VEC	[21]
	microemulsions composed of PEG-lipid/oleic acid/vitamin E/cholesterol	137~139nm	in M5076 tumor-bearing C57BL/6 mice	[61]
	telodendrimer (PEG(5k)-Cys(4)-L(8)-CA(8)) with disulfide cross-linked micelles	~ 16 nm	in lymphoma bearing mice	[42]
	ESM/cholesterol/PEG2000-ceramide/quercetin	~130 nm	MDA-MB-231 cell; in mice	[37]
	distearoylphosphatidylethanolamine-PEG liposomes (DSPE-PEG)	~100 nm	RM-1 prostate tumor cell; DBA/2 mice; BDF1 mice	[35]
	egg sphingomyelin/cholesterol/PEG2000-ceramide/quercetin	~130 nm	JIMT-1 human breast-cancer cell; in mice	[62]
	phospholipon100H/cholesterol/PEG2000	110~130 nm	athymic mice	[63]
Dextran sulphate	dextran sulfate complex solid lipid nanoparticles	100~169 nm	MDA-MB-231 cell; rat	[37]
	dextran sulphate-PLGA hybrid nanoparticles	~128 nm	MCF-7/Adr cell; rat	[52]
Oleic acid	vincristine–oleic acid ion-pair complex loaded submicron emulsion	145~170nm	MCF-7 cell; rat	[36]
	microemulsions composed of PEG-lipid/oleic acid/vitamin E/cholesterol	137~139nm	in M5076 tumor-bearing C57BL/6 mice	[61]
Liposome	vincristine sulfate liposome injection (Marqibo®)	~100 nm	Rag2M mice; non-Hodgkin's lymphoma; glioblastoma; mantle cell lymphoma; beagle dog	[22, 30, 31, 39-41, 43, 45, 46, 64-67]
	distearoylphosphatidylethanolamine-PEG liposomes (DSPE-PEG)	~100 nm	RM-1 prostate tumor cell; DBA/2 mice; BDF1 mice	[35]
	sphingomyelin and cholesterol liposomes	-	diffuse large B cell lymphoma; B cell non-Hodgkin's lymphoma	[32]
	egg sphingomyelin/cholesterol/PEG2000-ceramide/quercetin	~130 nm	JIMT-1 human breast-cancer cell; in mice	[62]
	phospholipon100H/cholesterol/PEG2000	110~130 nm	athymic mice	[63]
Chitosan	PLGA loaded collagen-chitosan complex film	-	-	[60]
PBCA	poly (butylcyanoacrylate) nanoparticles modified superficially with Pluronic® F-127	-	raji cell; mice	[68]
Transfersomes	vincristine loaded transfersomes	~63 nm	in rat	[69]
Niosome	niosomal vincristine	-	in rat	[70, 71]

Table 2. Vinblastine delivery systems.

Material	Formula	Size	Treatment	Reference
Thymidine conjugate	vinblastine-thymidine (Covalent Bond)	Molecular level	K562, HT29, and MCF7 cell lines	[19]
Folic acid and folate	desacetylvinblastine monohydrazide attached to a hydrophilic folic acid-peptide compound(EC145) (Covalent Bond)	Molecular level	novel synthesis study and the clinical pharmacokinetics and exposure-toxicity relationship study	[77, 79]
	vinblastine-folate by carbohydrate-based synthetic approach(EC0905) (Covalent Bond)	Molecular level	novel synthesis study and invasive urothelial carcinoma in dogs	[80-82]
	vinblastine sulfate-loaded folate-conjugated bovine serumalbumin nanoparticles	~150 nm	novel synthesis study	[83]
PLGA	vinblastine encapsulated in PLGA microspheres	46 μm	pharmacokinetics study	[84]
Liposome	anti-HER2 immunoliposomal vinblastine	99.5 nm	SKBR-3 and BT474-M2 *in vitro* and BT474-M2 xenografts in mice	[85]
	magnetic cationic liposomes packaged vinblastine	105-267 nm	B16-F10 *in vitro* and in mice	[74, 78]
	anionic liposomes (DPPC and DPPG with cholesterol)	-	six cell lines tested	[86]
	new liposome formulations (wheat germ lipids)	-	against nine human leukemic cell lines	[87]
	multi-lamellar vesicle-liposomes	-	UV-2237M murine fibrosarcoma and its Adriamycin (ADR)-selected multidrug resistant (MDR) variants.	[88]

Table 3. Vinorelbine delivery system.

Material	Formula	Size	Treatment	Reference
Lipid microsphere	vinorelbine lipid microsphere vehicle	~180 nm	reduce inflammation in ear-rim auricular vein injection rabbit	[89]
Lipid emulsion	vinorebine incorporated in lipid emulsion	~165 nm	A549, Heps G2 and BCAP-37 in mice	[90]
Liposome	temperature-sensitive liposome packed vinorebine	~100 nm	Lewis lung carcinoma in mice	[96]
	^{111}In-labeled VNB-PEGylated liposomes	-	C26/tk-luc colon carcinoma in mice	[100]
	PEGylated liposome formulations	-	drug loading and pharmacokinetic studies；HT-29、BT-474 and Calu-3 in mice	[92, 101]
	immuno-liposomes using anti-CD166 scFv	-	Du-145, PC3, and LNCaP *in vitro*	[102]
PE	micelles packed vinorebine (PEG-PE)	~14 nm	4T1 tumor in mice	[99]
PEG	aptamer-nanoparticle (AP-PLGA-PEG)	<200 nm	MDA-MB-231 BC cells and MCF-10A *in vitro*	[103]
	PEGylated solid lipid nanoparticles	180-250 nm	MCF-7 and A549 cells *in vitro*	[104]
	^{111}In-labeled VNB-PEGylated liposomes	-	C26/tk-luc colon carcinoma in mice	[100]
	PEGylated liposome formulations	-	drug loading and pharmacokinetic studies；HT-29、BT-474 and Calu-3 in mice	[92, 101]
	micelles packed vinorebine (PEG-PE)	-	4T1 cells *in vitro*	[105]
PLGA	aptamer-nanoparticle (AP-PLGA-PEG)	<200 nm	MDA-MB-231 BC cells and MCF-10A *in vitro*	[103]
Lecithin E80 and oleic acid	solid lipid nanoparticles	150-350 nm	MCF-7 *in vitro*	[106]

carrier and reduce toxicity in mice.[94] Vinorelbine lipid microsphere vehicles reduce venous inflammation and have pharmacokinetics *in vivo* that are similar to the current vinorelbine aqueous injection.[89] In 2008, Xu *et al.* developed a lipid emulsion formula, another strategy for reducing inflammation in local injection sites. [95] Vinorelbine incorporated in lipid emulsion significantly reduced the decreases in red and white blood cells. In addition, the potential formula of a vinorelbine-phospholipid complex can dramatically reduce injection irritation and maintain an antitumor effect in lung and breast cancer in mouse models.[90] Temperature-sensitive liposome-packed vinorelbine can inhibit tumor growth much more efficiently than free vinorelbine after only 30 minutes of hyperthermia.[96] The PEG-phosphatidylethanolamine micelle containing hydrophobic and hydrophilic position is another widly used drug delivery system.[97-99] Lei *et al.* observed that the PEG-phosphatidylethanolamine micelle (14.5 nm in diameter) accumulated in the lymph node and reduced metastasis rate in 4T1 tumor bearing mice.[99]

5. VINDESINE AND VINFLUNINE

Vindesine, desacetyl-vinblastine-amide, is a semisynthetic vinca alkaloid with effects similar to those of vinblastine.[6, 107] Vindesine inhibits net tubulin addition at the assembly ends of microtubules and treats pediatric solid tumors; malignant melanoma; blast crisis of chronic myeloid leukemia; acute lymphocytic leukemia; metastatic colorectal; and breast, renal, and esophageal carcinomas.[6, 108, 109] Although vindesine is useful for treating many types of cancer, it is not approved by the FDA.[6] Vinflunine, a semisynthetic vinca alkaloid, is currently being clinically evaluated.[6, 110] Both second-generation vinca alkaloid, vinorelbine, and third-generation compound vinflunine have shown promising results in cancer therapy.[110] Vinflunine is emerging as an effective anticancer agent because it is less neurotoxic than vinorelbine and has superior antitumour activity (preclinical) compared to that of other vinca alkaloids. Although vindesine and vinflunine are promising antitumor agents used clinically, research on related drug delivery systems is limited.

6. COMBINATION THERAPY

Combination therapy is a promising strategy for reducing the side effects of vinca alkaloids, [20] which are combined with other chemotherapy drugs to enhance antitumor effects (Table **4**). Drugs are often administered simultaneously as a cocktail or sequentially to maximize their therapeutic impact.[111] Vincristine combined with cyclophosphamide and prednisone is called CVP, which is used as a first-line therapy for follicular B-cell lymphoma.[111-114] A combination of cyclophosphamide, doxorubicin, vincristine, and prednisone, called CHOP, is used in front-line therapy to treat patients with either follicular or diffuse large B-cell lymphoma.[111-114] Rituximab combined with CVP or CHOP creates another first-line treatment for patients with diffuse large B-cell lymphoma and follicular lymphoma.[111-114]

Vinblastine can be used to treat different kinds of tumors when in combination with other chemotherapy agents. Vinblastine, cisplatin, and radiation therapy, known as VCRT, is used to treat IIIA and IIIB non-small-cell lung cancer.[115] Cisplatin, doxorubicin, cyclophosphamide, vinblastine, and bleomycin, or CISCA/VB, is used in patients with disseminated nonseminomatous germ-cell tumors.[116] Combination therapy with doxorubicin, bleoycin, vinblastine, and dacarbazine is a standard chemotherapy regimen for Hodgkin's lymphoma.[117]

Table 4. Combination therapy of vinca alkaloids for cancer treatments

Formula	Applications	Reference
CVP (cyclophosphamide, vincristine and prednisone)	first-line therapy for follicular B-cell lymphoma	[111-114]
CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone)	front line therapy for follicular or diffuse large B-cell lymphoma	[111-114]
rituximab combine with CVP or CHOP	first-line therapy for diffuse large B-cell lymphoma and follicular lymphoma	[111-114]
VCRT (vinblastine, cisplatin and radiation therapy)	treat IIIA and IIIB non-small-cell lung cancer	[115]
CISCA/VB (cisplatin, doxorubicin, cyclophosphamide, vinblastine and bleomycin)	non-seminomatous germ-cell tumors	[116]
ABVD (doxorubicin, bleoycin, vinblastine and dacarbazine)	standard chemotherapy for Hodgkin lymphoma	[117]
vinorelbine and cisplatin	adjuvant chemotherapy for non-small cell lung cancer	[118-121]
a thoracic radiation scheme, vinorelbine and cisplatin	stage III A and stage III B non-small cell lung cancer	[122]

Vinorelbine combination chemotherapy is also used to treat various cancers. Vinorelbine plus cisplatin is used for non-small-cell lung cancer. [118-121] A novel thoracic radiation scheme was developed in 2014 that combined vinorelbine and cisplatin; patients with stage III A and stage III B non-small-cell lung cancer subjected to this type of chemotherapy exhibited positive results. [122]

CONCLUSION

Vinca alkaloids are a class of anticancer drugs used as chemotherapy reagents for many kinds of tumors; however, their side effects restrict application. Drug delivery systems and combination therapy could reduce these side effects. This paper presents a review of drug delivery systems, including liposome-entrapped drugs, chemical- or peptide-modified drugs, polymeric packaging drugs, and chemotherapy drug combination therapy. Liposome-entrapped drugs have protective effects, harmless to tissues at the injection site, and can also enhance the half-life of drugs. Target specific antigens, such as HER-2 receptor or CD166, were

modified to the liposome, which enhanced the binding ability and reduced toxicity to other organs. Combination therapy could reduce the side effects; we have described various combinations such as CVP, CHOP, and VCRT. Although vindesine and vinflunine are promising vinca alkaloids, but descriptions of their drug delivery systems are few. Based on the successful drug delivery systems with vincristine, vinblastine, and vinorelbine, researchers can develop new formulas for vindesine and vinflunine in the future.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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