Drug Delivery Systems and Combination Therapy by Using Vinca Alkaloids

Chun-Ting Lee¹, Yen-Wei Huang¹, Chih-Hui Yang² and Keng-Shiang Huang¹,*

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

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, vinceristine, 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, hypotension, 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, vinceristine, vinblastine, vinorelbine, vindesine, and vinflunine, and one of the vincamine, vinpocetine (Fig. 2), have clinical uses (however, in the United States, only vinceristine, vinblastine, and vinorelbine have been approved for clinical use [6]). Researchers have isolated vinblastine in 1958, [7] and later synthesized vinceristine, 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 antitumorogenic 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,
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 neovascular 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].
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 lymphoblastic 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 bio-compatibility, 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]

### 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/MEP-PLA)              | ~153 nm      | CT-26 lung metastasis mice; HU-VEC                                        | [21]      |
|                                  | microemulsions composed of PEG-lipid/oleic acid/vitamin E/cholesterol   | 137–139 nm   | in MS076 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]      |
|                                  | distearoylphosphatidyethanolamine-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       | 145–170 nm   | MCF-7 cell; rat                                                            | [36]      |
|                                  | microemulsions composed of PEG-lipid/oleic acid/vitamin E/cholesterol   | 137–139 nm   | in MS076 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] |
|                                  | distearoylphosphatidyethanolamine-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 (butylicanoacrylate) nanoparticles modified superficially with Pluronics® 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, Hep G2 and BCAP-37 in mice               | [90]      |
| Liposome                         | temperature-sensitive liposome packed vinorelbine | ~100 nm  | Lewis lung carcinoma in mice                   | [96]      |
|                                 | 111In-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 mouse                            | [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]     |
|                                 | 111In-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 widely 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 alkaloids, 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]

Vinorelbine 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, bleomycin, 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] |
| VCR (vinblastine, cisplatin and radiation therapy) | treat IIIA and IIIB non-small-cell lung cancer | [115] |
| CISCA/VA (cisplatin, doxorubicin, cyclophosphamide, vinblastine and bleomycin) | non-seminomatous germ-cell tumors | [116] |
| ABVD (doxorubicin, bleomycin, 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 IIIA and stage IIIB 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.

ACKNOWLEDGEMENTS

This work was financially supported by a grant from the Ministry of Science and Technology, Taiwan.

REFERENCES

[1] Catharanthus roseus. http://en.wikipedia.org/wiki/Catharanthus_roseus.

[2] Wang, C.H.; Wang, G.C.; Wang, Y.; Zhang, X.Q.; Huang, X.J.; Zhang, D.M.; Chen, M.F.; Ye, W.C., Cytotoxic dimeric indole alkaloids from Catharanthus roseus. Fitoterapia, 2012, 83(4), 765-769.

[3] Nayak, B.S.; Anderson, M.; Pinto Pereira, L.M., Evaluation of wound-healing potential of Catharanthus roseus leaf extract in rats. Fitoterapia. 2007, 78(7-8), 540-544.

[4] Nayak, B.S.; Pinto Pereira, L.M., Catharanthus roseus flower extract has wound-healing activity in Sprague Dawley rats. BMC Complement. Altern. Med. 2006, 6, 41.

[5] Patel, Y.; Vadgama, V.; Baxi, S.; Chandrabhanu; Tripathi, B., Evaluation of hypolipidemic activity of leaf juice of Catharanthus roseus (Linn.) G. Donn. in guinea pigs. Acta Pol. Pharm., 2011, 68(6), 927-935.

[6] Moudi, M.; Go, R.; Yien, C.Y.; Nazre, M., Vinca Alkaloids. Adv. Drug Deliv. Rev., 2011, 63(10), 1231-1235.

[7] Noble, R.L.; Beer, C.T.; Cutts, J.H., Further biological activities of vinca leukoblastine - an alkaloid isolated from Vinca rosea (L.). Biochem. Pharmacol., 1958, 1, 347-348.

[8] Svetobor, G.H., Alkaloids of Vinca rosea Linn. IX. Extraction and characterisation of leurosidine and leucocristine. Lloydia, 1961, 24, 173-178.

[9] Johnson, S.A.; Harper, P.; Hortobagyi, G.N.; Pouillart, P., Vinorelbine: an overview. Cancer Treat. Rev., 1996, 22(2), 127-142.

[10] Sen, K.; Mandal, M., Second generation liposomal cancer therapeutics: transition from laboratory to clinic. Int. J. Pharm. Sci., 2013, 4(481), 28-43.

[11] Ueda, K.; Cardarelli, C.; Gottesman, M.M.; Pastan, I., Expression of a full-length cDNA for the human “MDR1” gene confers resistance to colchicine, doxorubicin, and vinblastine. Proc. Natl. Acad. Sci. USA, 1987, 84(9), 3004-3008.

[12] Allen, T.M.; Cullis, P.R., Liposomal drug delivery systems: from concept to clinical applications. Adv. Drug Deliv. Rev., 2013, 65(1), 36-48.

[13] Torchilin, V., Tumor delivery of macromolecular drugs based on the EPR effect. Adv. Drug Deliv. Rev., 2011, 63(3), 131-135.

[14] Zhang, M.; Shi, X., Folic acid-modified dendrimer-DOX conjugates for targeting cancer chemotherapy. J. Control. Release. 2013, 172(1), 655-656.

[15] Gregoriadis, G., The carrier potential of liposomes in biology and medicine (second of two parts). N. Engl. J. Med., 1976, 295(14), 765-770.

[16] Gregoriadis, G., The carrier potential of liposomes in biology and medicine (first of two parts). N. Engl. J. Med., 1976, 295(13), 704-710.

[17] Yu, D.H.; Lu, Q.; Xie, J.; Fang, C.; Chen, H.Z., Peptide-conjugated biodegradable nanoparticles as a carrier to target paclitaxel to tumor neovasculature. Biomaterials, 2010, 31, 2278-2292.

[18] Chen, J.; Li, S.; Shen, Q., Folic acid and cell-penetrating peptide conjugated PLGA-PEG bifunctional nanoparticles for vincristine sulphate delivery. Eur. J. Pharm. Sci. : Official J. Eur. Federation Pharm. Sci., 2012, 47(2), 430-443.

[19] Aspland, S.E.; Ballatore, C.; Castillo, R.; Deshamaria, J.; Eustaquito, T.; Goettel, P.; Guo, Z.; Li, Q.; Nelson, D.; Sun, C.; Castellino, A.J.; Newman, M.J., Kinase-mediated trapping of bi-functional conjugates of paclitaxel or vinblastine with thymidine in cancer cells. Bioorg. Med. Chem. Lett., 2006, 16(9), 5194-5198.

[20] Song, W.; Tang, Z.; Li, M.; Lv, S.; Sun, H.; Deng, M.; Liu, H.; Chen, X., Polyopeptide-based combination of paclitaxel and cisplatin for enhanced chemotherapy efficacy and reduced side-effects. Acta Biomaterialia, 2014, 10(3), 1392-1402.

[21] Wang, C.; Zhao, M.; Liu, Y.R.; Luan, X.; Guan, Y.Y.; Lu, Q.; Yu, D.H.; Bai, F.; Chen, H.Z.; Fang, C., Suppression of colorectal cancer subcutaneous xenograft and experimental lung metastasis using nanoparticle-mediated drug delivery to tumor neovasculature. Biomaterials, 2014, 35(4), 1215-1226.

[22] O’Brien, S.; Schiller, G.; Lister, J.; Damon, L.; Goldberg, S.; Aultzky, W.; Ben-Yehuda, D.; Stock, W.; Coutre, S.; Douer, D.; Heffner, L.T.; Larson, M.; Seiter, K.; Smith, S.; Assouline, S.; Kuriakose, P.; Maness, L.; Nagler, A.; Rowe, J.; Schaich, M.; Shiplberg, O.; Yee, K.; Schmieder, G.; Silverman, J.A.; Thomas, D.; Deitcher, S.R.; Kantarjian, H., High-dose vincristine sulfate liposome injection for advanced, relapsed, and refractory adult Philadelphia chromosome-negative acute lymphoblastic leukemia. J. Clin. Oncol. : Official J. Am. Soc. Clin. Oncol., 2013, 31(6), 676-683.

[23] Kruczynski, A.; Hill, B.T., Vinflunine, the latest Vinca alkaloid in clinical development. A review of its preclinical anticancer properties. Crit Rev. Oncology/Hematology, 2001, 40(2), 159-173.

[24] Hill, B.T., Vinflunine, a second generation novel Vinca Alkaloid with a distinctive pharmacological profile, now in clinical development and prospects for future mitotic blockers. Curr. Pharm. Des., 2001, 7(13), 1199-1212.

[25] Braguer, D.; Barret, J.M.; McDaid, H.; Kruczynski, A., Antitumor activity of vinflunine: effector pathways and potential for synergies. Seminars Oncol., 2008, 35(Suppl 3), S13-21.

[26] Noble, R.L., The discovery of the vinca alkaloids–chemotherapeutic agents against cancer. Biochem. Cell Biol. = Biochimie et Biologie Cellulaire, 1990, 68(12), 1344-1351.

[27] Ng, J.S., Vinflunine: review of a new vinca alkaloid and its potential role in oncology. J. Oncol. Pharm. Pract. : Official Publication Int. Soc. Oncol. Pharm. Practitioners, 2011, 17(3), 209-224.

[28] Schutz F.A.; Bellmunt, J.; Rosenberg, J.E.; Choueiri, T.K., Vinflunine, a second generation novel Vinca Alkaloid: drug safety evaluation of this novel synthetic vinca alkaloid. Expert Opin Drug Saf., 2011, 10(4), 645-653.

[29] Silverman, J.A.; Deitcher, S.R., Marqibo® (vincristine sulfate liposome injection) improves the pharmacokinetics and pharmacodynamics of vincristine. Cancer Chemother. Pharmacol., 2013, 71(3), 555-564.

[30] Harrison, T.S.; Lyseng-Williamson, K.A., Vincristine sulfate liposome injection: a guide to its use in refractory or relapsed acute lymphoblastic leukemia. BioDrugs: Clin. Immunother. Biopharm. Gene Therapy, 2013, 27(1), 69-74.

[31] Davis, T.; Farag, S.S., Treating relapsed or refractory Philadelphia chromosome-negative acute lymphoblastic leukemia: liposome-encapsulated vincristine. Int. J. Nanomedicine, 2013, 8, 3479-3488.

[32] Boehlke, I.; Winter, J.N., Sphingomyelin/cholesterol liposomal vincristine: a new formulation for an old drug. Expert Opin. Biol Ther., 2006, 6(4), 409-415.

[33] Thomas, D.A.; Sarris, A.H.; Cortes, J.; Faderl, S.; O’Brien, S.; Giles, F.J.; Garcia-Manero, G.; Rodriguez, M.A.; Cabanillas, F.; Kantarjian, H., Phase II study of sphingosamine vincristine in patients with recurrent or refractory adult acute lymphocytic leuke- mia. Cancer, 2006, 106(1), 120-127.

[34] Yang, F.; Wang, H.; Liu, M.; Hu, P.; Jiang, J., Determination of free and total vincristine in human plasma after intravenous administration of vincristine sulfate liposome injection using ultra-high performance liquid chromatography tandem mass spectrometry. J. Chromatography A, 2013, 1275, 61-69.

[35] Cui, J.; Li, C.; Wang, C.; Li, Y.; Zhang, L.; Xiu, X.; Wei, N., Development of pegylated liposomal vincristine using novel sulfobutyl ether cyclodextrin gradient: is improved drug retention sufficient to surpass DSPE-PEG-induced drug leakage? J. Pharm. Sci., 2011, 100(7), 2385-2388.
Aboutaleb, E.; Atyabi, F.; Khoshayand, M.R.; Vatanara, A.R.; Osama, S.N.; Kobarbared, F.; Ding, R.; Improved brain delivery of vincristine using dextran sulfate complex solid lipid nanoparticles: Optimization and in vivo evaluation. J. Biomed. Mat. Res. A, 2013.

Bedikian, A.Y.; Papadopoulos, N.E.; Kim, K.B.; Vardeleoni, A.; Smith, T.; Lu, B.; Deitcker, S.R., A pilot study with vincristine sulfate formulation in patients with metastatic melanoma. Mela-noma Res., 2008, 18(6), 400-404.

Rodriguez, M.A.; Pylik, R.; Kozak, T.; Chhanabhai, M.; Gas-croyne, R.; Lu, B.; Deitcker, S.R.; Winter, J.N., Vincristine sulfate liposomes injection (Marqibo) in heavily pretreated patients with refractory aggressive non-Hodgkin lymphoma: report of the pivotal phase 2 study. Cancer, 2009, 115(3), 3475-3482.

Wong, M.Y.; Chiu, G.N., Simultaneous liposomal delivery of quercetin and vincristine for enhanced estrogen-receptor-negative breast cancer treatment. Anti-Cancer Drugs, 2010, 21(4), 401-410.

Pathak, P.; Hess, R.; Weiss, M.A., Liposomal vincristine for relapsed or refractory Ph-negative acute lymphoblastic leukemia: a review of literature. Therapeut. Adv. Hematol., 2014, 5(1), 18-24.

Kato, J.; Li, Y.; Xiao, K.; Lee, J.S.; Luo, J.; Tuscano, J.M.; O'Don-nell, R.T.; Lam, K.S., Disulfide cross-linked micelles for the targeted delivery of vincristine to B-cell lymphoma. Mol. Pharm., 2012, 9(6), 1727-1735.

Kaplan, L.D.; Deitcker, S.R.; Silverman, J.A.; Morgan, G., Phase II study of vincristine sulfate liposome injection (Marqibo) and rituximab for patients with relapsed and refractory diffuse large B-cell lymphoma or mantle cell lymphoma in need of palliative therapy. Clin. Myeloma, Myeloma Leuk., 2014, 14(1), 37-42.

Xi, G.; Rajaram, V.; Mania-Farnell, B.; Mayanil, C.S.; Soares, M.B.; Tomita, T.; Goldman, S., Efficacy of vincristine administration by convection-enhanced delivery in a rodent brainstem tumor model documented by bioluminescence imaging. Child's Nerv. Syst.: ChNS: Official J. Int. Soc. Pediatric Neurosurgery, 2012, 28(4), 565-574.

Ozeki, T.; Kaneko, D.; Hashizawa, K.; Imai, Y.; Tagami, T.; Okada, H., Improvement of survival in C6 rat glioma model by a sustained drug release from localized PLGA microspheres in a thermoreversible hydrogel. Int. J. Pharma., 2012, 427(2), 299-304.

Hagemeister, F.; Rodriguez, M.A.; Deitcker, S.R.; Younes, A.; Fayed, L.; Gov, A.; Dang, N.H.; Forman, A.; McLaughlin, P.; Medeiros, L.J.; Pro, B.; Romaguera, J.; Samaniego, F.; Silverman, J.A.; Sarris, A.; Cabanillas, F., Long term results of a phase 2 study of vincristine sulfate liposome injection (Marqibo(®)) substituted for non-liposomal vincristine in cyclophosphamide, doxorubicin, vincristine, prednisone with or without rituximab for patients with untreated aggressive non-Hodgkin lymphomas. Br. J. Haematol., 2013, 162(5), 631-638.

Sun, Y.; Xu, L.; Zhang, Q.; Zhou, H., The controlled release study of Vincristine Sulfate. Artificial Cells, Blood Substitutes, Immo bilization Biotechnol., 2003, 31(1), 81-88.

Yang, C.H.; Huang, K.S.; Grinnemeier, A.M.; Wang, C.Y.; Tseng, S.C.; Chen, S.Y.; Lin, Y.H.; Lin, Y.S., Synthesis of uniform poly(D,l-lactide) and poly(D-lactide-co-glycolide) microspheres using a microfluidic chip for comparison. Electrophoresis, 2013.

Lin, Y.S.; Yang, C.H.; Wu, C.T.; Grinnemeier, A.M.; Wang, C.Y.; Hsieh, W.C.; Chen, S.Y.; Huang, K.S., A microfluidic chip using phenol formaldehyde resin for uniform-sized polycaprolactone and chitosan microspheres generation. Molecules, 2013, 18, 6521-6531.

Lin, Y.S.; Yang, C.H.; Wang, C.Y.; Chang, F.R.; Huang, K.S., Hsieh, W.C., An Aluminum Microfluidic Chip Fabrication Using a Convenient Micromilling Process for Fluorescent Poly(DL-lactide-co-glycolide) Microspheres Generation. Sensors-BASEL, 2012, 12, 655-655-1467.

Yang, C.H.; Huang, K.S.; Lin, Y.S.; Lu, K.; Tseng, C.C.; Wang, E.C.; Lin, C.H.; Wu, Y.H.; Chang, J.Y., Microfluidic assisted synthesis of multi-functional polycaprolactone microcapsules: incorporation of CdTe quantum dots, Fe3O4 superparamagnetic nanoparticles and tamoxifen anticancer drugs. Lab. Chip, 2009, 9(7), 961-965.
Noble, C.O.; Guo, Z.; Hayes, M.E.; Marks, J.D.; Park, J.W.; Zu, Y.; Zhang, Y.; Zhao, X.; Zhang, Q.; Liu, Y.; Jiang, R., Optimi-

Vlahov, I.R.; Santhapuram, H.K.; You, F.; Wang, Y.; Kleindl, P.J.; Maswadeh, H.; Demetzos, C.; Dimas, K.; Loukas, Y.L.; Geor-

Dandamudi, S.; Campbell, R.B., The drug loading, cytotoxicity and tumor vascular targeting characteristics of magnetite in magnetic drug targeting. *Biomaterials*, 2007, 28(31), 4673-4683.

Vacc, A.; lurlaro, M.; Ribanti, D.; Minischetti, M.; Nico, B.; Ria, R.; Pellegrino, A.; Dammacco, F. Antiangiogenesis is produced by nontoxic doses of vinblastine. *Blood*, 1999, 94(12), 4143-4155.

Faneca, H.; Faustino, A.; Pedroso de Lima, M.C., Synergistic anti-

tumor effect of vinblastine and HSV-Tk/GCV gene therapy mediated by albumin-associated cationic liposomes. *J. Control. Re-

Li, J.; Sausville, E.A.; Klein, P.J.; Morgenstern, D.; Leonam, C.P.; Messmann, R.A.; LoRusso, P., Clinical pharmacokinetics and ex-

Yanagawa, A.; Mizushima, Y.; Komatsu, A.; Horiuchi, M.; Yanagawa, A.; Mizushima, Y.; Komatsu, A.; Horiuchi, M.; Takenaga, M., Application of lipid microspheres for the treatment of cancer. *Lipid Microspheres*, 1996, 20(6B), 209-219.

Xu, L.; Pan, J.; Chen, Q.; Yu, Q.; Chen, H.; Xu, H.; Qiu, Y.; Yang, S., External magnet improves antitumor effect of vinblastine and the suppression of metastasis. *Cancer Sci.*, 2009, 100(8), 1537-1543.

Li, S.; Hahn, S.J.; Vaughn, J.F.; Reno, D.S.; Leonam, C.P., Carbohydrate-

Dhawan, D.; Ramos-Vara, J.A.; Naughton, J.F.; Cheng, L.; Low, P.S.; Rothenbuhler, R.; Leonam, C.P.; Parker, N.; Klein, P.J.; Vlah-

Zu, Y.; Zhang, Y.; Zhao, X.; Zhang, Q.; Liu, Y.; Jiang, R., Optimization of the preparation process of vinblastine sulfate (VBLS)-

Marinina, J.; Shenderova, A.; Mallory, S.R.; Schwendeman, S.P., Stabilization of vincristine and vinorelbine encapsulated in poly(lactide-co-

Noble, C.O.; Guo, Z.; Hayes, M.E.; Marks, J.D.; Park, J.W.; Benz, C.C.; Kirpotin, D.B.; Drummond, D.C., Characterization of highly stable liposomal and immunoliposomal formulations of vincristine and vinblastine. *Cancer Chemother. Pharmacol.*, 2009, 64(4), 741-751.

Mawsedh, H.; Demetzos, C.; Dimas, K.; Loukas, Y.L.; Georgopoulo-

Mawsedh, H.; Hatziantonious, S.; Demetzos, C.; Dimas, K.; Georgopoulos, A.; Ralli, M., Encapsulation of vinblastine into new liposome formulations prepared from triticum (wheat germ) lipids and its activity against human leukaemic cell lines. *J. Pharm. Pharmacol.*, 2002, 54(2), 189-196.

Seid, C.A.; Fidler, J.I.; Clyné, R.K.; Earnest, L.E.; Fan, D., Overcoming marine tumor cell resistance to vinblastine by presentation of the drug in multilamellar liposomes consisting of phosphatidyl-

choline and phosphatidylserine. Selective cancer therapies, 1991, 7(3), 103-112.

Zhang, H.Y.; Tang, X.; Li, H.Y.; Liu, X.L., A lipid microsphere vehicle for vinorelbine: Stability, safety and pharmacokinetics. *Int. J. Pharma.*, 2008, 349(1), 70-79.

Fan, M.; Zhao, H.; Luo, Y.; Lin, X.; Xu, L.; He, H.; Xu, H.; Tang, X., Evaluation of the efficacy, toxicity and safety of vinorelbine in-

Li, Y.; Jin, W.; Yan, H.; Liu, H.; Wang, C., Development of intrave-

Dandamudi, S.; Park, J.W.; Guo, Z.; Noble, C.O.; Wu, C.J.; Tseng, Y.L.; Hong, K.; Kirpotin, D.B., Improved phar-

Lee, W.C.; Chang, C.H.; Huang, C.M.; Wu, Y.T.; Chen, L.C.; Ho, C.L.; Chang, T.J.; Lee, T.W.; Tsai, T.H., Correlation between ra-

Takenaga, M., Application of lipid microspheres for the treatment of cancer. *Lipid Microspheres*, 1996, 20(6B), 209-219.

Xu, L.; Pan, J.; Chen, Q.; Yu, Q.; Chen, H.; Xu, H.; Qiu, Y.; Yang, S., External magnet improves antitumor effect of vinblastine and the suppression of metastasis. *Cancer Sci.*, 2009, 100(8), 1537-1543.

Bae, Y.H.; Yin, H., Stability issues of polymeric micelles. *J. Control. Release : Official J. Control. Release Soc.*, 2008, 131(1), 2-4.

Tang, N.; Du, G.; Wang, N.; Liu, C.; Hang, H.; Liang, W., Improv-

Tu, T.; Chao, C.Y.; Lin, Y.Y.; Chang, C.H.; Lu, Y.C.; Hwang, J.J.; Tseng, R.J.X., In vivo evaluation of the biocompatibility and safety of liposomes for vinorelbine bitartrate. *Drug Deliv.*, 2009, 16(2), 56-62.

Roth, A.; Drummond, D.C.; Conrad, F.; Hayes, M.E.; Kirpotin, D.B.; Benz, C.C.; Marks, J.D.; Liu, B., Anti-CD166 single chain antibody-mediated intracellular delivery of liposomal drugs to prostate cancer cells. *Mol. Cancer Ther.*, 2007, 6(10), 2737-2746.

Zhao, H.; Liu, J.; Ding, J., Antitumor-nanoparticles enhance intracellular delivery of vinorelbine to breast cancer cells. *J. Drug Target.*, 2014, 22(1), 57-66.

Wan, F.; You, J.; Sun, Y.; Zhang, X.G.; Cui, F.D.; Du, Y.Z.; Yuan, C., Preparation and characteristic of vinorelbine bitartrate-loaded solid lipid nanoparticles. *Int. J. Pharma.*, 2008, 349(1), 104-110.

Li, Y.; Jin, W.; Yan, H.; Liu, H.; Wang, C., Development of intrave-

Tian, X.; Cui, C.; You, J.; Cui, F.D.; Du, Y.Z.; Yuan, C., Prepara-

Xu, L.; Pan, J.; Chen, Q.; Yu, Q.; Chen, H.; Xu, H.; Qiu, Y.; Yang, S., External magnet improves antitumor effect of vinblastine and the suppression of metastasis. *Cancer Sci.*, 2009, 100(8), 1537-1543.

Bae, Y.H.; Yin, H., Stability issues of polymeric micelles. *J. Control. Release : Official J. Control. Release Soc.*, 2008, 131(1), 2-4.

Tang, N.; Du, G.; Wang, N.; Liu, C.; Hang, H.; Liang, W., Improv-

Tu, T.; Chao, C.Y.; Lin, Y.Y.; Chang, C.H.; Lu, Y.C.; Hwang, J.J.; Tseng, R.J.X., In vivo evaluation of the biocompatibility and safety of liposomes for vinorelbine bitartrate. *Drug Deliv.*, 2009, 16(2), 56-62.

Roth, A.; Drummond, D.C.; Conrad, F.; Hayes, M.E.; Kirpotin, D.B.; Benz, C.C.; Marks, J.D.; Liu, B., Anti-CD166 single chain antibody-mediated intracellular delivery of liposomal drugs to prostate cancer cells. *Mol. Cancer Ther.*, 2007, 6(10), 2737-2746.

Zhao, H.; Liu, J.; Ding, J., Antitumor-nanoparticles enhance intracellular delivery of vinorelbine to breast cancer cells. *J. Drug Target.*, 2014, 22(1), 57-66.
bulle dynamics and cell proliferation in vitro. *Cancer research, 1985, 45*(6), 2741-2747.

[109] Joel, S., The comparative clinical pharmacology of vincristine and vindesine: does vindesine offer any advantage in clinical use? *Cancer Treat. Rev., 1996, 21*(6), 513-525.

[110] Simoen, C., New vinca alkaloids in cancer treatment. http://www.hospitalpharmacyeurope.com/featured-articles/new-vinca-alkaloids-cancer-treatment 2006.

[111] DiJoseph, J.F.; Dougher, M.M.; Evans, D.Y.; Zhou, B.B.; Damle, N.K., Preclinical anti-tumor activity of antibody-targeted chemotherapy with CMC-544 (inotuzumab ozogamicin), a CD22-specific immunoconjugate of calicheamicin, compared with non-targeted combination chemotherapy with CVP or CHOP. *Cancer Chemother. Pharmacol., 2011, 67*(4), 741-749.

[112] Lugtenburg, P.; Silvestre, A.S.; Rossi, F.G.; Noens, L.; Krall, W.; Bendall, K.; Szabo, Z.; Jaeger, U., Impact of febrile neutropenia risk assessment and management in patients with diffuse large B-cell lymphoma treated with R-CHOP regimens. *Clin. Lymphoma, Myeloma Leuk., 2012, 12*(5), 297-305.

[113] Michallet, A.S.; Coiffier, B., Recent developments in the treatment of aggressive non-Hodgkin lymphoma. *Blood Rev., 2009, 23*(1), 11-23.

[114] Pettengell, R.; Johnsen, H.E.; Lugtenburg, P.J.; Silvestre, A.S.; Duhnsen, U.; Rossi, F.G.; Schwenkglenks, M.; Bendall, K.; Szabo, Z.; Jaeger, U., Impact of febrile neutropenia on R-CHOP chemotherapy delivery and hospitalizations among patients with diffuse large B-cell lymphoma. *Support. Care Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer, 2012, 20*(3), 647-652.

[115] Waters, E.; Dingle, B.; Rodrigues, G.; Vincent, M.; Ash, R.; Dar, R.; Incula, R.; Kocha, W.; Malthaner, R.; Sanatani, M.; Stitt, L.; Yaremko, B.; Yonous, J.; Yu, E., Analysis of a novel protocol of combined induction chemotherapy and concurrent chemoradiation in unresected non-small-cell lung cancer: a ten-year experience with vinblastine, cisplatin, and radiation therapy. *Clin. Lung Cancer, 2010, 11*(4), 243-250.

[116] Fizazi, K.; Do, K.A.; Wang, X.; Finn, L.; Logothetis, C.J.; Amato, R.J.; Logothetis, C.J.; Amato, R.J., A 20% dose reduction of the original CISCA/VB regimen allows better tolerance and similar survival rate in disseminated testicular non-semionomatous germ-cell tumors: final results of a phase III randomized trial. *Ann. Oncol.: Official J. Eur. Soc. Med. Oncol./ESMO, 2002, 13*, 125-134.

[117] Schwenkglenks, P.R.; Szucs, T.D.; Culakova, E.; Lyman, G.H., Hodgkin lymphoma treatment with ABVD in the US and the EU: neutropenia occurrence and impaired chemotherapy delivery. *J. Hematol. Oncol., 2010, 3*, 27.

[118] Ramsey, S.D.; Moinpour, C.M.; Lovato, L.C.; Crowley, J.J.; Grevstad, P.; Presant, C.A.; Rivkin, S.E.; Kelly, K.; Gandara, D.R., Economic analysis of vinorelbine plus cisplatin versus paclitaxel plus carboplatin for advanced non-small-cell lung cancer. *J. Natl. Cancer Inst., 2002, 94*(4), 291-297.

[119] Pepe, C.; Hasan, B.; Winton, T.L.; Seymour, L.; Graham, B.; Livingston, R.B.; Johnson, D.H.; Rigas, J.R.; Ding, K.; Shepherd, F.A., Adjuvant vinorelbine and cisplatin in elderly patients: National Cancer Institute of Canada and Intergroup Study JBR.10. *J. Clin. Oncol.: Official J. Am. Soc. Clin. Oncol., 2007, 25*(12), 1553-1561.

[120] Kreuter, M.; Vansteenkiste, J.; Griesinger, F.; Hoffmann, H.; Dienemann, H.; De Leyn, P.; Thomas, M., Trial on refinement of early stage non-small cell lung cancer. Adjuvant chemotherapy with pemetrexed and cisplatin versus vinorelbine and cisplatin: the TREAT protocol. *BMC Cancer, 2007, 7*, 77.

[121] Reinmuth, N.; Meyer, A.; Hartwigen, D.; Schaeper, C.; Huebner, G.; Skoek-Lober, R.; Bier, A.; Gerecke, U.; Held, C.P.; Reck, M., Randomized, double-blind phase II study to compare nitroglycerin plus oral vinorelbine plus cisplatin with oral vinorelbine plus cisplatin alone in patients with stage IIB/IV non-small cell lung cancer (NSCLC). *Lung Cancer, 2014, 83*(3), 363-368.

[122] Imamura, F.; Konishi, K.; Uchida, J.; Nishino, K.; Okuyama, T.; Kumagai, T.; Kawaguchi, Y.; Nishiyama, K., Novel chemoradiation with concomitant boost thoracic radiation and concurrent cisplatin and vinorelbine for stage III A and III B non-small cell lung cancer. *Clin Lung Cancer, 2014, 15*(4), 281-6.