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REVIEW ON PHARMACOKINETICS OF VINBLASTINE DRUG AND ITS DELIVERY SYSTEM

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ABSTRACT

Vinblastine belongs to a class of a drug vinca alkaloids which is a chemical analogue of vincristine. The four major vinca alkaloids that are now used clinically include vinblastine, vincristine, vindesine and vinorelbine. They have been used to treat both Hodgkin and non-Hodgkin lymphomas breast cancer and germ cell tumour. Microtubules are component of cell that provide structural framework that enables cells to divide and grow. Vinblastine act as anti-microtubule agent and produced anticancer affects by causing abnormalities in microtubule formation in cells. This incomplete microtubule formation caused by vinblastine affect the cellular replication and inhibits the process of cell division due to which cell death occur. At the end we will discuss some precision based drug delivery systems which has proved to be very effective in loading drug to its target tissue.

KEYWORDS: Vinblastine, Anti-cancer drug, Microtubules, Drug delivery system, DNA Nanostructures, DNA origami, Leptosomes.

BACKGROUND

Vinblastine is a vinca-alkaloids that has a molecular formula of $C_{46}H_{58}N_4O_9$ and molar mass of 810.975g/mole.[1] this drug is been isolated from naturally occurring compound that has been derived from periwinkle plant catharanthusroseus G.donot.[2] They were first discovered in 1950 by Canadian scientist Robert Nobel and Charles Beer.

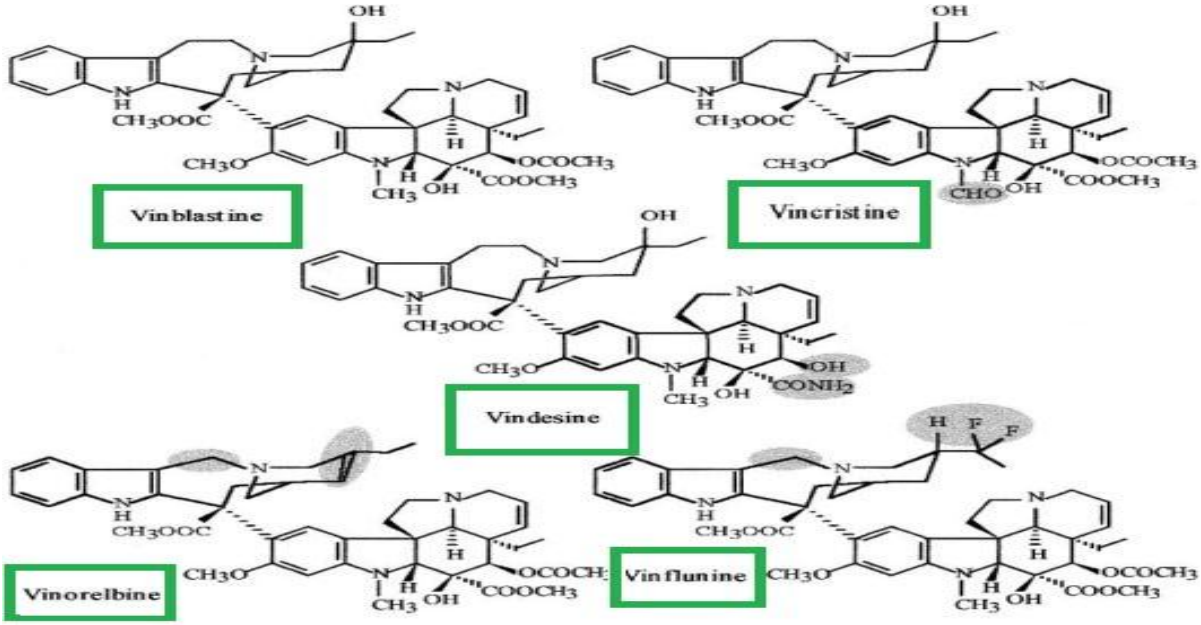

Figure 1: https://www.sciencedirect.com/science/article/pii/S1572599506800414.

Microtubules are very important structure that appear during the process of cell division. It plays an important role in cellular processes like vesicle Transportation, cell structure, motility, signalling and division of the cell. This assembly creates a special arrangements called as centrosomes located near the nuclear membrane.[3] Because microtubules are very important in assembly and disassembly of spindle fibres. Drugs that bind to this tubulin are very important because these kinds of drugs can inhibit chromosomes segregation and block cell division. Vinblastine that attaches to tubulin protein and block the process of chromosomes segregation and cell division. Vinblastine may also DNA RNA and protein synthesis all of which can lead to cell death.[4] The assembly and disassembly of the mitotic spindle during the process of cell division has makes itself to be a very good target for the development of anticancerous drug.

Microtubule being the target of many anticancer drugs most of which originate from natural products has made it simply the single best anticancer drug identified up to now. Microtubule are made of from head to tail addition of alpha beta-tubulin heterodimers that are arranged parallel to a cylindrical axis to form tubes of 25nm diameter. This drug acts by attaching to tubulin heterodimer and thus preventing the formation of mitotic spindle due to which cell proliferation stops.[5]

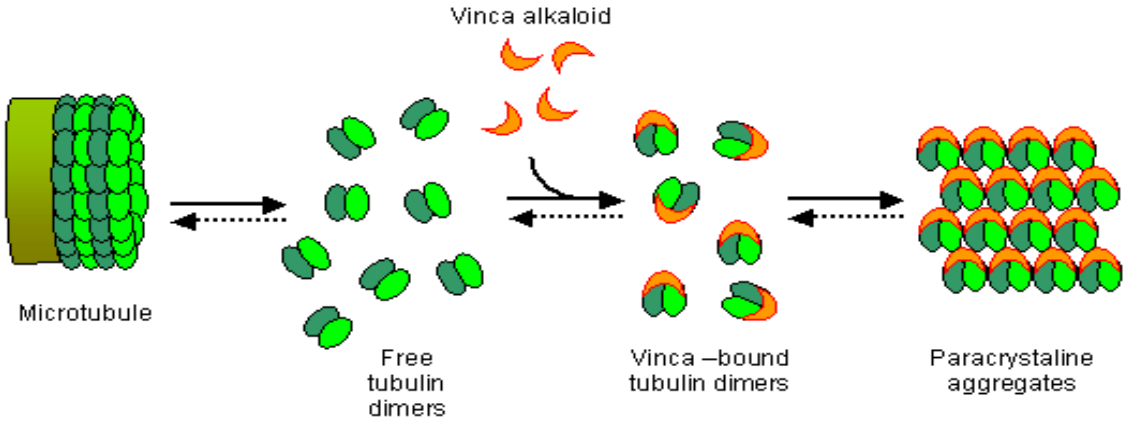

Figure 2: http://www.ncbi.nlm.nih.gov.proxy medicina.unito.it/PubMed/15057285.

It is mainly prescribed for the treatment of cancers such as renal cell carcinoma, breast, colon and small cell cancers.[6] Vinblastine is known to have been distributed throughout the body. Maximum plasma concentration is 7.95g/mole.[7] As the drug mainly binds to plasma proteins it causes the excretion to be very slow and because of high rate of function of hepatobiliary system the concentration of vinblastine is found 5-100 times in bile as compared to blood.[8] Because of high molecular weight of vinblastine it is considered to have a very complex structure.[9] Vinblastine is available in the market under the brand name velban or vinacleukobastine its excretion mainly occurs through biliary system and through kidney.[10]

Mechanism of action of drug and dynamics of Microtubule

Microtubules are polymer of tubulin protein almost found in almost all dividing eukaryotic cells. The cytotoxicity of vinca alkaloids is because of their association with tubulin protein due to which interruption of microtubule function occur and metaphase arrest occur.[11] The polymerization dynamics of microtubules are central to the biological function because it provides some special conformational arrangements to the cell due to which cell can change rapidly in response to cellular need and to perform mechanical work properly. For the purpose of polymerization microtubule used a special energy molecule GTP.[12,13,14] there are two behaviour that play an important role in polymerization and depolymerisation of microtubule. The first one is tread milling that is growth at one end and shortening at the other end and the other one is dynamic instability. Both these behaviour play an important role in assembly and disassembly of mitotic spindle especially the high dynamic microtubule is more important for adherence of spindle to chromosomes, motility of chromosomes, separation at anaphase and proper alignment at metaphase plate.[15] The binding site of vincaalkaloids to tubulin is different from other drug that are used to stop the process of cell division. The reaction of vinblastine to tubulin is so fast and binding is reversible irrespective of temperature. The domain to which vinblastine binds is known as vincadomain.[16] Association of vinblastine to tubulin cause a conformational change in tubulin forming vinblastine –tubulin oligomer which is the main step toward the metaphase arrest.[17,18,19]

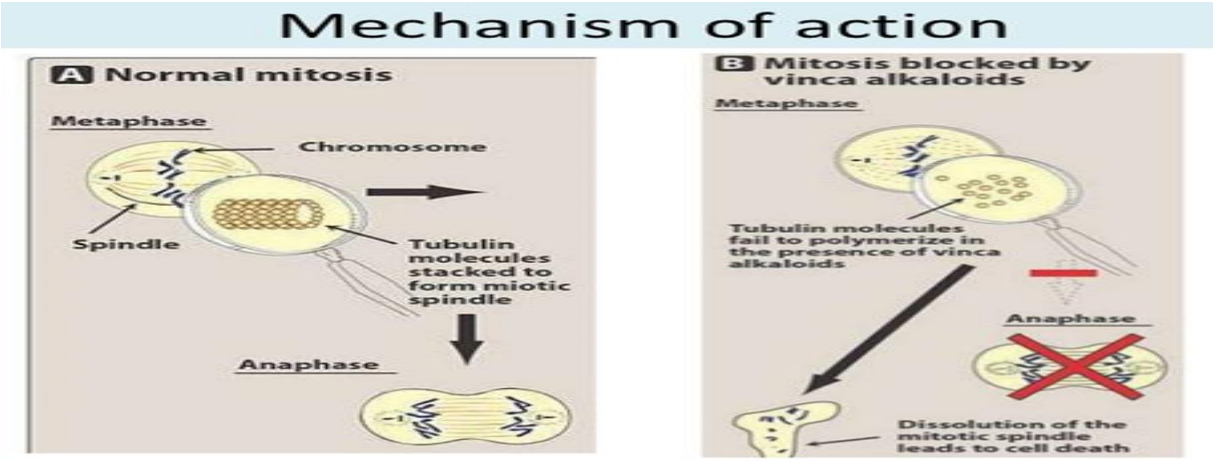

Figure 3: http://www.rroij.com/open-access/pharmacological-activity-of-vinca-alkaloids-.pdf.

Vinblastine clogs and decelerate the process of mitosis at metaphase-anaphase transition in different cells. The clogging effect is because of microtubule depolymerisation which is then followed by nuclear envelope. Breakdown due to which no spindle will be formed and chromosomes remain scattered within the cells.

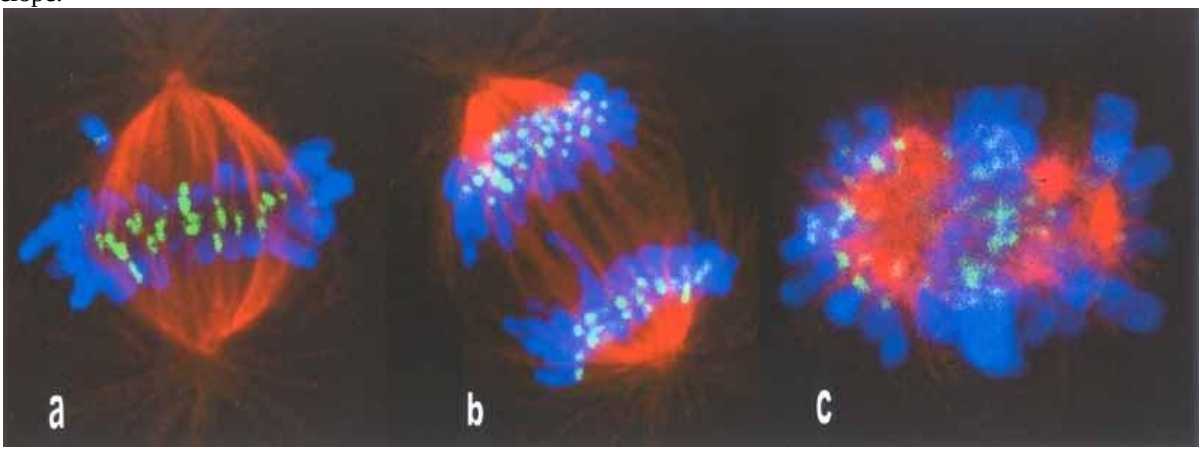

Figure 4: Development of different stages of cell cycle with the addition of microtubule inhibiting drug.

The blue colour shows the chromosome, green colour shows the kinetochore and the red colour shows the microtubule.

1. Shows the early metaphase that are form by the condensation of microtubule.
2. Shows he replication of chromosome and after replication moving of the spindle to two daughter cells occur.
3. Shows the chromosomes remains at the pole and do not segregate.

The duration of the clogging effect is about up to 50hrs that results in chromosomes decompensation and ultimately apoptosis of cell occurs.[20]

How is vinblastine given (administered)?

Vinblastine is administered into a vein (intravenous) by a short injection (1-15) minutes on a weekly basis and the dose mainly depends on condition being treated, the age of the patient, the particular regimen being used, and the overall health of the patient. If it escapes from the vein in which it is administered it may cause serious damage to the tissue. Although patients will be monitored for this, they should tell their healthcare provider immediately if they experience pain, redness or swelling at the site in which the drug is being administered. In addition, patients may experience an allergic-type reaction with the administration of vinblastine. Patients experiencing shortness of breath or closing of the throat should tell their healthcare provider immediately.[21]

Pharmacokinetics and Excretion

It is not well known that what is the major route of excretion of vinblastine but some evidence shows that its excretion mainly occurs through the biliary system.[22]

Up to now the only metabolite that is discovered for vinblastine is desacetylvinblastine and for vinorelbine the metabolite is desacetylvinorelbine. The presence of desacetylvinblastine has been confirmed in the urine and stool of patient who received vinblastine. The concentration of this metabolite was found very low in urine and stool representing about 1% of total dose in both excreta. Similarly, another vincaalkaloids member

vinorelbine metabolite concentration has also been confirmed in the urine and stool but the concentration compare to DAB (desacetylvinblastine) was very low representing the total dose of 0.25% in excreta. At the same time very less or no concentration has been confirmed in the blood. Minor metabolite like 3-6-epoxyvinorelbine and 11 other minor metabolites has also been confirmed in the urine of patient.[23,24,25] The enzyme that is mainly involved in the metabolism of is also identified. Isoenzymecytochrome (CYP) P450 3A4 has been identified as a main metabolism factor of vinblastine.[26] Anti CYP3A polyclonal antibodies and cyclosporine is identified as inhibitor of the whole vinca-alkaloids family. Conjugation reaction was also done for vinblastine but either of glucuronide or Sulphates was not found in the patient urine and blood.[27] The transporter that had so far confirmed for the transport of this drug across the cell is adenosine triphosphate binding cassette transporter.[28]

Metabolism

Metabolism is mainly done by hepatocytes. Vinblastine has been shown to be mediated by hepatic cytochrome P4503A isoenzyme (CYP). It has been estimated that its metabolism mainly occurs in liver and in liver it is converted into desacetylvinblastine which is more active than the parent compound on weight basis.[29]

Safety issues related with the use of drug

Apart from being a very good microtubule inhibitor the vinca alkaloids have some serious effects also on the cell ranges from mild to severe. All the vinca-alkaloids have the ability to cause neurotoxicity but compare to other vinca alkaloids vincristine is more effective in causing neurotoxicity and cause vincristine neurotoxicity can lead to severe motor and sensory neuropathy.[30] Axonal degradation and axonal transport is the first pathological effect that is caused by vinca alkaloid. Although the uptake of vincristine to the brain is very low but if it gets into the brain it can cause depression, hallucination, agitation, insomnia, seizure, confusion, mental state changes, coma and improper secretion of antidiuretics hormone. To overcome these toxicities level different antidotes have been used that include vitamin B_{12}, thiamine, folinic acid, pyridoxine and neuroactive agent but the result that came was not up to the mark and these agents didn't show any proper effect to decreased the level of toxicity. Low level of neutrophils has been observed with the use of all vinca alkaloids but specifically with the use of with the use of vinblastine the level was bit more. Severe hematologic effect and myelosuppression has also been reported with the use of vincristine. With the use of vinca alkaloids gastrointestinal toxicity has also been observed. Abdominal pain, bloating, constipation, Raynaud phenomena, acute cardiac ischemia, acute pulmonary effect, hand foot syndrome, hepatic toxicity, nausea, vomiting, diarrhoea has also been reported with the use of vinca-alkaloids.[31]

Because these drugs cause the weakness of immune system, it is prescribed that these drugs should not be used during the time of pregnancy or if someone is planning for pregnancy. The concentration or dose of drug, treatment duration, health of patient determines the accumulation and cytotoxicity of these drugs.[32]

Medical applications of Vinblastine

Being a good microtubule inhibitor the vinblastine can be used for many purpose some of which include the treatment of testicular carcinoma, advanced Hodgkin lymphoma and non-advanced Hodgkin lymphoma, lymphocytic lymphoma. It can also be used for the treatment of breast cancer, germ cell tumours, histiocytic lymphoma, advanced mycosis fungoid, advanced testicular cancer, Kaposi sarcoma and choriocarcinoma.[33]

Precision Based Drug Delivery Systems

Different types of drug delivery vehicles have been made so far which had overcome up to some extent their side effects. We will discuss here some of them.

Different methods are used to enhance the drug efficiency and are revolutionized by the help of nanotechnology. **Nanoparticles having a large surface to volume ratio** and **small size** can bind and absorb easily. Small size also favours them to easily cross the blood brain barrier, achieve more solubility inside the cell, enter the pulmonary system and be absorbed in the tight junction of endothelial cells and also the new formulation of existing drugs drives the pharmaceutical companies by creating more market value and benefited the patients.[34,35]

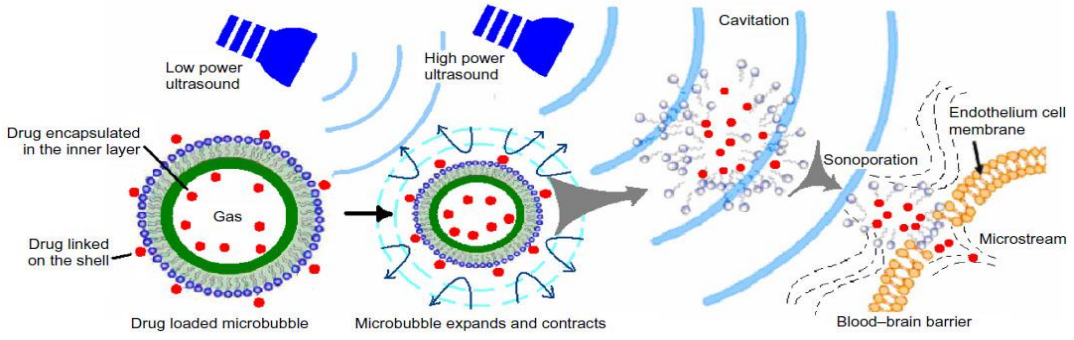

Figure 5: *h*ttps://www.dovepress.com/current-approaches-to-enhance-cns-delivery-of-drugs-across-the-brain-b-peer-reviewed-fulltext-article-IJN.

Nanoscale compounds based on proteins, lipids, and synthetic polymers, organic and inorganic carrier have been used as drug delivery vehicle. In comparison with direct administration of the drug if the drug is encapsulated in some kind of carrier it can enhance drug stability, targeted drug delivery, decreased side effects, protection from degradation in blood stream, better drug stability and can improve pharmacokinetics and pharmacodynamics of drug.[36]

Liposomes are small spherical lipid based bilayer vesicle that can carry a drug or small molecules to a specific target. Since their discovery in 1956 they have been widely used as drug delivery vehicle due to their biodegradable and biocompatible nature. Due to their lipoic bilayer structure liposomes has the ability to integrate a drug both in aqueous core and lipid bilayer. Incorporating the drug in aqueous or making the use of lipoic bilayer of liposome we can control the pharmacokinetics and pharmacodynamics of drug. Different drug clinically approved by based on liposomes include DOXIL/Calyx (doxorubicin) AMBISOME (amphotericin B).in designing the liposomes the vesicle size is very important. The only disadvantage that is related with the use of liposomes is their complex and costly production requirements.[37]

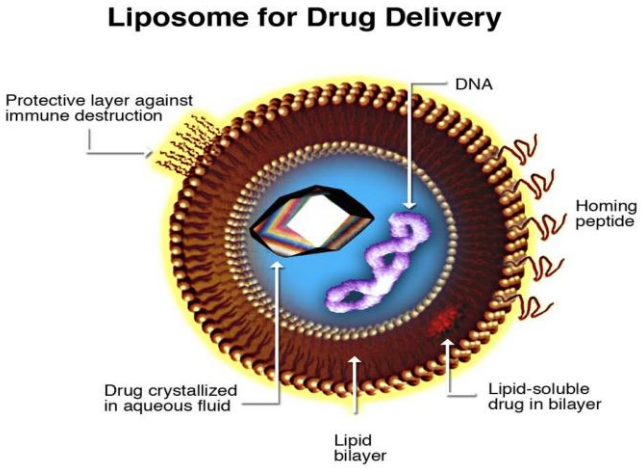

Figure 6: Torchilin, V (2006). "Multifunctional Nano carriers". Advanced Drug Delivery Reviews. 58 (14): 1532–55. doi:10.1016/j.addr.2006.09.009. PMID 17092599

Another method is the **use of structural DNA nanotechnology** and **especially DNA origami techniques** which scientists believe that it may revolutionize the subject of drug delivery in upcoming years.DNA origami is the folding of DNA at nanoscale to frame a three or two dimensional shape at nanoscale. The self-assembly and self-complementarily of ssDNA has made this interaction possible.[38] Because of their biocompatible and bio degradable nature they are the most promising nanostructure for the delivery of drug and also they can be modified into different aptamers.[39]

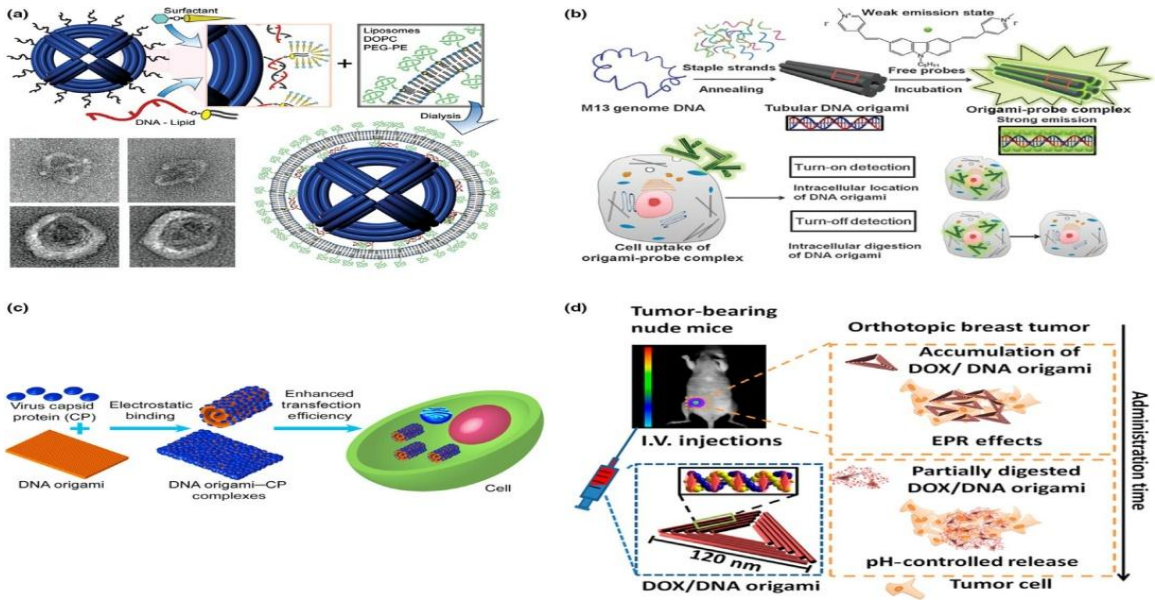

Fig. 7: DNA origami nanostructures as drug carriers.

1. DNA octahedron (blue) encapsulated inside lipid bi-layer. Top panels, transmission electron microscopy images of free octahedrons; bottom panels, transmission electron microscopy images of lipid encapsulated octahedrons. Reproduced from Perrault and Shih (2014), with permission from [American Chemical Society].
2. Fluorescently labelled DNA origami tubes for cellular tracking. Reproduced from Shen *et al.* (2012), with permission from [American Chemical Society].
3. Virus capsid protein (CP; blue) covered DNA origami rectangles(orange). Reproduced from Mikkila *et al.* (2014), with permission from [Royal Society of Chemistry].
4. Doxorubicin (DOX)-containing DNA origami triangles showing enhanced permeability and retention (EPR) effects. Reproduced from Zhang *etal* (2014), with permission from [American Chemical Society]

The stability of any nanostructure in the physiological environment is very important because as soon as the molecule carrier get enter into the blood it gets destroyed by nucleases. But in case of DNA nanostructure it has been shown that it has greater stability for nucleases. Scientists believe that stability against nucleases is because of different shape and conformation of DNA nanostructures that reduce the effect and accessibility of nucleases.[40] Enhancement in anticancer activity and long lasting accumulation properties at the of tumour has been showed through the use of DNA origami nanostructure and especially with the use of triangular DNA origami nanostructure in association with Doxorubicin resulted in high apoptosis rate of Doxorubicin-resistant breast cancer cells. Cellular elimination rate of doxorubicin was also studied which showed that the elimination rate of DNA origami nanostructure was fast as compare to the drug which was not bound with DNA nanostructure. No weight loss, decreased tumour size, and less toxicity was observed in the mice when Doxorubicin DNA containing structure was used.[41.42]

The **Specific binding of antibody to its specific receptor** has made antibody a good tool for drug delivery system. As antibody recognize only their specific cell surface receptor it makes them a promising molecule for proper targeting.GD2 and ScFv are the common antibodies used for targeted miRNA delivery. For lung metastasis ScFv-modified LPH nanoparticle has also been made as a carrier of miRNA.[43,44]

CONCLUSION

The only problem with the use of anticancer drug is their cytotoxicity. Adverse side effects, development of multi drug resistance, low therapeutic indices, high dose requirements, poor bioavailability and non-specific targeting are the characteristics feature that play an important role in the process of cytotoxicity. Precise drug delivery is very important because it can reduce these overall effects. The need of the day is to develop such kind of drug delivery vehicle that is easy to address and have the ability to carry that specific drug to its target site thereby produced therapeutic action and reduce the side effects by delivering the drug precisely.

Abbreviations

1. **GTP** (Guanosine-5'-triphosphate)
2. **SsDNA** (Single-Stranded DNA)
3. **Np** (Nanoparticle)
4. **ABC Transporter** (Adenosine Triphosphate Binding Cassette transporter)
5. **DAB** (Desacetylvinblastine)
6. **CYP** (Cytochrome P)
7. **ADH** (Antidiuretic Hormone)

Declaration

- **Ethics approval and consent to participate:** (Not Applicable)
- **Consent for publication**

(a) Neither the article nor portions of it have been previously published elsewhere.
(b) The manuscript is not under consideration for publication in another journal, and will not be submitted elsewhere.
(c) All authors consent to the publication of the manuscript in Pakistan Journal of Pharmaceutical Sciences.

Availability of data and materials: (Not Applicable)

Competing interests

The Author(s) declare no competing interest.

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Authors' contributions

All authors have contributed equally.

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REFERNCES

1. Van der Heijden, Robert; Jacobs, Denise I.; Snoeijer, Wim; Hallard, Didier; Verpoorte, Robert "The Catharanthus alkaloids: Pharmacognosy and biotechnology". Current Medicinal Chemistry, 2004; 11(5): 607–628. doi:10.2174/0929867043455846. PMID 15032608.
2. Johnson. I. S., Armstrong, J. G. Gorman. M.. and Burnett, J. P.. Jr. The Vinca alkaloids: a new class of oncolytic agents. Cancer Res., 1963; 23: 1390-1427.

3. Mitchison T., Kirschner M. W. Nature, 1984; 312: 237–242. [PubMed] [Google Scholar]
4. Goldman R. D. J. Cell Biol., 1971; 51: 752–762. [PMC free article] [PubMed] [Google Scholar]
5. Moudi M.; Go R.; Yien C. Y.; Nazre M. Vinca alkaloids. Int. J. Prev. Med, 2013; 4: 1231–1235. [PMC free article] [PubMed] [Google Scholar]
6. Li Z.; Alisaraie L. Microtubules dual chemo and thermoresponsivdepolymerization. Proteins, 2015; 8 3: 970–98110.1002/prot.24793.[PubMed] [CrossRef] [Google Scholar
7. Long Q.-Z.; Zhou M.; Liu X.-G.; Du Y.-F.; Fan J.-H.; Li X.; He D.-L. Interaction of CCN1 with αvβ3 integrin induces P-glycoprotein and confers vinblastine resistance in renal cell carcinoma cells. Anticancer Drugs, 2013; 24: 810–81710.1097/cad.0b013e328363046d. [PubMed] [CrossRef] [Google Scholar
8. Bau R.; Jin K. K. Crystal structure of vinblastine. J. Chem. Soc., Perkin Trans. 1, 2000; 2079–2082. 10.1039/b001855o. [CrossRef] [Google Scholar]
9. Zhou X. J.; Martin M.; Placidi M.; Cano J. P.; Rahmani R. In vivo and in vitro pharmacokinetics and metabolism of vincaalkaloids in rat II. Vinblastine and Vincristine. Eur. J. Drug Metab. Pharmacokinet, 1990; 15: 323–332. 10.1007/bf03190222. [PubMed] [CrossRef] [Google Scholar]
10. Bau R.; Jin K. K. Crystal structure of vinblastine. J. Chem. Soc., Perkin Trans. 1, 2000; 2079–2082. 10.1039/b001855o. [CrossRef] [Google Scholar]
11. "Vinblastine Sulfate". The American Society of Health-System Pharmacists. Archived from the original on 2015-01-02. Retrieved Jan 2, 2015.
12. Himes RH. Interactions of the catharanthus (Vinca) alkaloids with tubulin and microtubules. PharmacolTher, 1991; 51: 257–67. [PubMed] [Google Scholar]
13. Wordeman, L.; Mitchison, T.J. In: Microtubules, Hyams JS, Lloyd CW, eds. Wiley-Liss, New York, 1994; 287-302.
14. Wilson, L.; Jordan, M.A. In: Microtubules, Hyams J, Lloyd C, eds. John Wiley and Sons, Inc.; New York, 1994; 59-84.
15. McIntosh, J.R. In: Microtubules, Hyams JS, Lloyd CW, eds. Wiley-Liss, Inc, New York, 1994; 413-434.
16. Wilson, L.; Jordan, M.A. Chemistry and Biology, 1995; 2: 569-573.
17. Bai, R.B.; Pettit, G.R.; Hamel, E. J. Biol. Chem., 1990b; 265: 17141-17149.
18. Lobert, S.; Correia, J. In: Methods in Enzymology, 2000; 323: 77-103.
19. Fujiwara, K.; Tilney, L.G. Ann. N.Y. Acad. Sci., 1975; 253: 27-50.
20. Lobert, S.; Fahy, J.; Hill, B.T.; Duflos, A.; Etievant, C.; Correia, J.J. Biochemistry, 2000; 39: 12053-12062.
21. Palmer, C.G.; Livengood, D.; Warren, A.K.; Simpson, P.J.; Johnson, I.S. Experimental Cell Research, 1960; 20: 198- 265.
22. Kufe DW, Pollock RE, Weichselbaum RR, Bast RC, Gansler TS, Holland JF, et al. 6th ed. Hamilton (ON): BC Decker Inc. Holland-Frei cancer medicine. [Google Scholar], 2003.
23. Rosazza JPN, Duffel MW, El-Marakby S, Ahn SH. Metabolism of the Catharanthus alkaloids: from Streptomyces griseus to monoamine oxydase B. J Nat Prod, 1992; 55: 269-284.
24. Owellen RJ, Hartke CA, Hains FO. Pharmacokinetics and metabolism of vinblastine in humans. Cancer Res., 1977; 37: 2597-2602.
25. Jehl F, Quoix E, Levêque D, et al. Pharmacokinetic and preliminary metabolic fate of navelbine in humans as determined by high performance liquid chromatography. Cancer Res., 1991; 51: 2073-2076.
26. Puozzo C, Zorza G, Gimbaud R, et al. Metabolism of vinorelbine in human: clinical application [abstract]. Proc Am Assoc Cancer Res, 2000; 41: 280.
27. Zhou-Pan XR, Sérée E, Zhou XJ, et al. Involvement of human liver cytochrome P4503A in vinblastine metabolism: drug interactions. Cancer Res, 1993; 53: 5121-5126.
28. Owellen RJ, Hartke CA, Hains FO. Pharmacokinetics and metabolism of vinblastine in humans. Cancer Res., 1977; 37: 2597-2602.
29. Ho RH, Kim RB. Transporters and drug therapy: implications for drug disposition and disease. ClinPharmacolTher. 2005;78: 260-277.
30. Zhou-Pan XR, Sérée E, Zhou XJ, et al. Involvement of human liver cytochrome P4503A in vinblastine metabolism: drug interactions. Cancer Res., 1993; 53: 5121-5126.
31. Himes RH. Interactions of the catharanthus (Vinca) alkaloids with tubulin and microtubules. PharmacolTher, 1991; 51: 257–67. [PubMed] [Google Scholar]
32. Kufe DW, Pollock RE, Weichselbaum RR, Bast RC, Gansler TS, Holland JF, et al. 6th ed. Hamilton (ON): BC Decker Inc. Holland-Frei cancer medicine. [Google Scholar], 2003.
33. Johnson IS, Armstrong JG, Gorman M, Burnett JP., Jr The vinca alkaloids: A new class of oncolytic agents. Cancer Res., 1963; 23: 1390–427. [PubMed] [Google Scholar
34. Rowinsky EK, Donehower RC. Paclitaxel (taxol) N Engl J Med, 1995; 332: 1004–14. [PubMed] [Google Scholar]
35. Kohane D.S. Microparticles and nanoparticles for drug delivery. Biotechnol. Bioeng, 2007; 96(2): 203–209. [PubMed] [Google Scholar] [Ref list]
36. Emerich D.F., Thanos C.G. Targeted nanoparticle-based drug delivery and diagnosis. J. Drug Target, 2007; 15(3): 163–183. [PubMed] [Google Scholar] [Ref list]
37. Mo R, Jiang T, Gu Z. Recent progress in multidrug delivery to cancer cells by liposomes.

Nanomedicine, 2014; 9: 1117–1120. doi: 10.2217/nnm.14.62. [PubMed] [CrossRef] [Google Scholar]
38. Carugo, D., Bottaro, E., Owen, J., Stride, E. &Nastruzzi, C. Liposome production by microfluidics: potential and limiting factors. Scientific Reports 6(25876), 25876, 2016.
39. Seeman NC. Nucleic acid junctions and lattices. J TheorBiol, 1982; 99: 237–47. [PubMed] [Google Scholar]
40. Douglas SM, Bachelet I, Church GM. A logic- gated nanorobot for targeted transport of molecular payloads. Science, 2012; 335: 831–4. [PubMed] [Google Scholar]
41. Mei Q, Wei X, Su F et al Stability of DNA origami nanoarrays in cell lysate. Nano Lett., 2011; 11: 1477–82. [PMC free article] [PubMed] [Google Scholar]
42. Jiang Q, Song C, Nangreave J et al DNA origami as a carrier for circumvention of drug resistance. J Am ChemSoc., 2012; 134: 13396–403. [PubMed] [Google Scholar]
43. Zhang Q, Jiang Q, Li N et al DNA origami as an in vivo drug delivery vehicle for cancer therapy. ACS Nano, 2014; 8: 6633–43. [PubMed] [Google Scholar]
44. Z.A. Ahmad, S.K. Yeap, A.M. Ali, W.Y. Ho, N.B. Alitheen, M. Hamid, scFv antibody: principles and clinical application, Clin. Dev. Immunol, 2012; (2012): 980250.
45. Y. Chen, X. Zhu, X. Zhang, B. Liu, L. Huang, Nanoparticles modified with tumor-targeting scFv deliver siRNA and miRNA for cancer therapy, Mol. Ther, 2010; 18: 1650-1656.