Cancer Chemother. Pharmacol. 2, 229–232 (1979)

Cancer Chemotherapy and Pharmacology
© Springer-Verlag 1979

# Vindesine
# A Short Review of Preclinical and First Clinical Data

R. W. Dyke[1], R. L. Nelson[1], and W. P. Brade[2]

[1] The Lilly Laboratory for Clinical Research and Indiana University, School of Medicine, Wishard Memorial Hospital, Indianapolis, Indiana 46202, USA
[2] Klinisch-Wissenschaftliche Abteilung, Eli Lilly GmbH, D-6380 Bad Homburg, Federal Republic of Germany

VDS is a new semisynthetic vinca alkaloid, which can be prepared either from VBL sulfate or from desacetylvinblastine (B 2, H 1). It has a wider spectrum of antitumor activity than VBL in animal tumor test systems, and a toxicity somewhere between that of VCR and that of VBL [38, 41].

According to the structural formula of VDS (23 amino-4-deacetoxy-23-demethoxy-4-hydroxy-vincaleucoblastine sulfuric acid salt), the C-23 position of VDS has an amino group instead of the methoxy group in VBL, and the C-4 position of VBL is deacetylated and bears a hydroxy group in the VDS molecule. In contrast to VCR, the N-linked substituent in the vindoline portion of VDS and of VBL is a methyl group, and not a formyl group as in VCR.

Despite the minimal chemical differences within the vinca derivatives a high stereochemical specificity is required for specific antitumor activity: in the Ridgeway osteogenic sarcoma and in the Gardener lymphosarcoma the following order of antineoplastic activity was observed [1]. VCR; Vindesine=deacetylvinblastinehydrazide; Deacetylvinblastine; Dihydrovindesine; C-18-Decarbomethoxyvindesine; VBL.

VDS has a similar activity to VCR against the P 388 leukemia, the P 1534 (J) (sc) leukemia, and the CA-755 mammary carcinoma. VDS increased the median survival and lifespan of mice with B-15 melanoma to a greater extent than VCR and VBL. VDS, like VCR and VBL, showed almost no activity against the L1210 leukemia and against the Lewis lung carcinoma [1].

The apparent structure-activity relationship is paralleled by a structure-toxicity relationship among the vinca derivatives: The acute IV $LD_{50}$ values in mice for VCR, VDS, and VBL are 2.1 mg/kg, 6.3 mg/kg, and 10.0 mg/kg, respectively, which means that VDS is considerably less toxic than VCR, but more toxic than VBL [40, 41].

The symptoms of chronic toxicity of VDS in rats, dogs, and monkeys consist mainly in leukopenia, anemia, inhibition of spermatogenesis, and dystrophy of the intestinal mucosa [41], which suggests that VDS causes its essential toxicity in rapidly dividing cells such as intestinal mucosa and bone marrow cells.

No indications of structural or functional damage to nerve tissue was seen in the chronic studies with dogs and rats [41]. Since in phase-I studies some neurotoxic effects of VDS were seen [3, 4], and since neurotoxicity is recognized as a dose-limiting factor in the clinical use of VCR [6, 35, 42], animal models for assessing the neurotoxic potential of VDS would be very valuable. Special comparative studies have therefore been carried out in chickens, cats, and monkeys. Chickens treated with VCR for 4 weeks showed significant neurotoxic symptoms. In the comparative VDS group no other signs of toxicity than lethargy were found Todd et al. (submitted for publication). In cats and monkeys similar results, i.e., a lower neurotoxic potential of VDS than of VCR, were observed. Additionally, the time necessary to block in vitro fast axoplasmic transport of newly synthesized proteins was greater for VDS and VBL than for VCR, suggesting that the potency of VCR is twice that of VDS and VBL [27].

Tissue distribution studies indicate that VDS concentrations in rat peripheral nerve and spleen, lung, liver, lymph nodes, and other tissues except spinal cord and brain, rapidly built up to values several times higher than those in plasma [7]. H3-Vindesine was cleared from rat tissues with half-lives between 13 h (sciatic nerve), which is similar to the plasma half-life (16 h), and 45 h (brain) [7].

The abbreviations used in this paper are: VCR, vincristine; VBL, vinblastine; VDS, vindesine, desacetylvinblastine amide sulfate; CR, complete response; PR, partial response; MR, minimal response

*Reprint requests should be addressed to:* R. W. Dyke

0344-5704/79/0002/0229/$ 01.00

The apparent structure-toxicity and structure-activity relationships cannot be explained simply by the interaction of vinca derivatives with tubulin. The interaction with tubulin has been claimed as the responsible mechanism of cytolytic activity [28, 30, 37, 43], but it appears to occur in vitro with almost the same efficacy for the individual vinca compounds [31]. Additional factors acting in vivo seem to be involved in the biological activity of vinca alkaloids: S, the penetration rate of drugs through lipoid structures such as membranes and myelin, is determined by their physicochemical properties, which are significantly influenced by the polarity of acidic or basic substituents [17]. Since the $C_4$ and $C_{23}$ substituents of VDS differ chemically and in polarity from the corresponding VBL and VCR substituents, comparative pharmacokinetics of the vinca derivatives, as determined by Nelson and Dyke [10, 25] with a radioimmunoassay [34], may contribute to a better understanding of the biological effects of vinca alkaloids.

Radioimmunologically determined serum VDS concentrations in cancer patients followed a typical triphasic decay with time curve when the data were plotted semilogarithmically [10]. The triphasic serum decay curve is compatible with an open three-compartment model. The rapid initial decay half-life of VDS is only 0.038 h, and is followed by a $\beta$-phase half-life of 0.0822 h and a terminal elimination half-life of 24.33 h [10]. A comparison of the mean pharmacokinetic parameters in man [10] revealed a shorter $\beta$-phase half-life and a minor retention of VDS in tissues compared with VCR [10, 25].

The comparative pharmacokinetics of the vinca derivatives pose the question as to whether once-weekly administration, which is common for VCR and VBL, is correct for all the vinca alkaloids. The bolus IV dose of 3 mg/m$^2$ VDS once weekly was certainly well tolerated [9, 26]. Twice-weekly dosing of VDS was applied on spaced days by Dyke [9], and, on consecutive days by Mathé et al. [23]. Holland et al. [16] gave 24-h infusions of VDS and Tan et al. [39] used five daily injections of VDS. At present no direct comparison of toxicity has been made between the different administration schedules.

The limiting side effect of VDS is neutropenia [10, 23, 32]. Neutropenia is dose- and schedule-related [13], and changes in total white cell count and in the polymorphonuclear leukocyte count with time are similar to those caused by VBL [10].

The effect of VDS on thrombocytes seems to be more frequently a platelet-sparing effect [13] or thrombocytosis [9, 10, 32] than thrombocytopenia [23, 13] (after more than once-weekly administration).

Neurotoxic side effects are probably less in degree than with VCR [18, 11, 20, 44], and seem to be more severe when VDS has been given twice weekly instead of once weekly [11]. Up to 3 mg VDS/m$^2$ probalby has no intolerable side effects, since bone marrow depression and neurologic side effects are minimal with this dose [26]. Depression of deep tendon reflexes without any concomitant electroneurologic changes is the early and only consistent finding [26]. No change of muscle strength or vibration sensitivity, no motor impairment, and a normal sensory nerve action potential amplitude was seen after doses of VDS up to 3 mg/m$^2$ [26]. Paresthesia was noted in about 40% of patients [10, 9, 32, 33], and in some cases this was combined with muscle weakness and of prolonged duration [13]. Mild paresthesia, jaw pain, and myalgias not interfering with normal functioning were relatively frequently observed. Transient generalized musculoskeletal discomfort has also occurred. According to Young [44], the overall tolerance of VDS was considerably better than that of VCR, since on average 15 VDS doses (3–4 mg/m$^2$ per week) were tolerated.

Constipation is reported to occur with frequencies varying from 18% [10, 9, 32] to 87% [13]. Alopecia, often of the slowly progressing type, was observed on average in 50% of patients [10, 13, 32].

Less than 15% of patients experienced nausea, diarrhea [33, 13], and/or phlebitis [13]. A maculopapular skin rash appearing after two injections and disappearing as treatment continued [32] was seen in 3 of 47 patients [32], and was also observed by Mathé [23].

A summary of clinical trial data from investigators in the United States and Europe up to February 1978 [9] reveals a high proportion of remissions in acute lymphatic leukemia (15 CR+17 PR out of 78). This includes data from Mathé's group [23, 22], who obtained a 68% (CR+PR) response rate in acute lymphatic leukemia [21] and a 55% response rate (5 CR +1 PR out of 11) in blastic crisis of myeloid leukemia [21].

Most ALL patients, especially those with immunoblastic types of acute lymphoid leukemia and of lymphosarcoma, were sesistant to all previously available efficient drugs, including VCR [23]. In a group of 13 ALL patients with proven resistance to VCR, six CR and one PR were achieved, which suggests an absence of cross-resistance between VCR and VDS [22, 23]. This is supported by the findings of Krivit et al. [19], who with VDS in combination with prednisone and L-asparaginase obtained M 1 or M 2 marrow in 11 of 21 ALL patients resistant to VCR.

A response rate of about 30% was seen in acute myelomonocytic leukemia (AMML) (5 PR out of 13), Hodgkin lymphoma (5 PR out of 14), and non-Hodgkin lymphoma (4 CR+2 PR out of 19) according to the international clinical trial data [9]. This seems a some-

what higher response than those obtained by Gralla et al. [13], and by Mathé for Hodgkin and non-Hodgkin lymphomas [23].

One of the most promising results was obtained in breast cancer by Powles et al. [32], who achieved two CR, four PR, and five MR in 21 patients. In breast cancer with soft tissue involvement, lymph node involvement, and lung involvement, 36%, 57% and 36% responses were seen after VDS, which are higher than the single-agent response rates for VCR and VBL [32].

The results obtained in lung cancer are also encouraging. A partial response rate of 22% was achieved in 46 patients with lung cancer, with an average duration of 5 months in adenocarcinoma [13]. The response rates obtained in non-small-cell carcinoma were similar to those obtained in small-cell carcinoma (2 CR+1 PR/8) [13]. Considering that all lung cancer patients who entered the phase-II study had received extensive prior therapy including VCR, the response rates with VDS seem to be comparable to those obtained with combination chemotherapy with conventional agents [13, 5]. Very recently, Young [44] reported response rates of 45% (18 PR/40) in lung cancer after treatment with a combination of VDS and cis-diaminodichloroplatinum.

Further responses were seen in testicular carcinoma (2 PR/13) [9] and in esophageal carcinoma (2 PR/5) [9]. In melanoma response rates of 20% (4 PR/21 (46), 1 CR+4 PR/23 [33] have been obtained: VDS seems to be especially useful in advanced melanoma with visceral disease [33], where response to DTIC is uncommon [12].

The different toxicity profiles the apparently absent cross-resistance in certain tumors [39, 18, 23], and the differences in oncolytic activity of the vinca derivatives [38] all still defy explanation on the grounds of their interaction with either polymerizing or preformed microtubules [15, 8] in malignant and nonmalignant cells [2, 37]. Possibly vinca alkaloids interact not only with tubulin but also with high-molecular-weight proteins associated with tubulin and necessary for microtubule activity [8, 2, 37]. Because of their differently polar substituents they may also reach their effector sites at different times and in different concentrations. In addition, various metabolites, some of which may or may not have a neurotoxic potential and/or antitumor activity [29] may contribute to the clinical effects and side effect of vinca alkaloids.

In summary, phase-I studies and phase-II studies have demonstrated antitumor activity against such advanced hematologic tumors as acute lymphatic leukemia, acute myelomonocytic leukemia, and blastic crisis of CML, and against such solid tumors as lung cancer, breast cancer, and melanoma. Phase-III studies are in progress.

In some advanced acute lymphoblastic leukemia patients who are resistant to VCR [39, 18, 23] and in some solid tumor patients who are resistant to VBL [24], VDS apparears to lack cross-resistance with the two naturally occurring vinca alkaloids, as it can induce remissions in these patients. The toxicity of VDS is seen mainly in hematopoietic depression, which limits the therapeutic dosage, and mild neurotoxicity.

## References


1. Barnett, C. J., Cullinan, G. J., Gerzon, K., Hoying, R. C., Jones, W. E., Newlon, W. M., Poore, G. A., Robinson, R. L., Sweeney, M. J., Todd, G. C.: Structure-activity relationships of dimeric catharanthus alkaloids. 1. Deacetylvinblastine amide (vindesine) sulfate. J. Med. Chem. **21**, 88 (1978)
2. Bensch, K. G., Malawista, S. E.: Microtubule crystals in mammalina cells. J. Cell Biol. **40**, 95 (1969)
3. Blum, R. H., Dawson, D. M.: Vindesine (V) – Phase I study of vinca alkaloid. Proc. Am. Assoc. Cancer Res./Am. Soc. Clin. Oncol. **17**, 108 (1976)
5. Bodey, G. P., Freireich, E. J.: Initial clinical studies of vindesine (desacetyl vinblastine amide sulfate). Proc. Am. Assoc. Cancer Res./Am. Soc. Clin. Oncol. **17**, 128 (1976)
5. Bodey, G. P., Lagakos, S. W., Gutierrez, A. C., et al.: Therapy of advanced squamous carcinoma of the lung: cyclophosphamide versus "COMB". Cancer **39**, 1026–1031 (1977)
6. Casey, E. B., Jellife, A. M., Lequesne, P. M., Millett, Y. L.: Vincristine neuropathy: Clinical and electrophysiological observations. Brain **96**, 69 (1973)
7. Culp, H. W., Daniels, W. D., McMahon, R. E.: Disposition and tissue levels of ($^3$H) vindesine in rats. Cancer Res. **37**, 3053 (1977)
8. Dentler, W. L., Granett, S., Rosenbaum, J. L.: Ultrastructural localization of the high molecular weight proteins associated with in vitro-assembled brain microtubules. J. Cell Biol. **65**, 237 (1975)
9. Dyke, R. W.: Present status of vindesine safety and efficacy data. In: Proceedings of the International Workshop of Vindesine, July 7, 1978. Stuttgart: Thieme (in press) 1979
10. Dyke, R. W., Nelson, R. L.: Phase I anti-cancer agents. Vindesine (desacetyl vinblastine amide sulfate). Cancer Treat. Rev. **4**, 135 (1977)
11. Dyke, R. W., Nelson, R. L.: Phase I-II clinical investigation of vindesine (desacetyl vinblastine amide sulfate, DVA). Curr. Chemother. **2**, (Abstract 640) (1978)
12. Einhorn, L. H., Furnas, B.: Combination chemotherapy for disseminated malignant melanoma with DTIC, vincristine, and methyl-CCNU. Cancer Treat. Rep. **61**, 881–883 (1977)
13. Gralla, R. J., Tan, C. T. C., Young, C. W.: Review of Phase-II Studies of vindesine at the Memorial Sloan-Kettering Cancer Center. In: Proceedings of the First International Workshop of Vindesine, July 7, 1978. Stuttgart: Thieme (in press) (1979)
14. Hargrove, W. W.: Preparation and activities of chemically modified dimeri catharanthus alkaloids. Lloydia **27**, 340 (1964)
15. Himes, R. H., Kersey, R. N., Heller-Bettinger, I., Samson, F. E.: Action of the vinca alkaloids vincristine, vinblastine, and desacetyl vinblastine amide in microtubules in vitro. Cancer Res. **36**, 3798 (1976)
16. Holland, J. F., Adrejczuk, A., Grenspan, E.: Initial clinical and pharmacological studies with vindesine: i.v. bolus versus 24-hrs infusion. Proc. Am. Assoc. Cancer Res. 129 (Abstract) (1978)
17. Korolkovas, A.: Grundlagen der molekularen Pharmakologie. (Essentials of Molecular Pharmacology). p. 80. Stuttgart: Thieme/Frankfurt: Wiley (1974)

18. Krivit, W., Hammond, D.: Vindesine: a phase II study by the Childrens Cancer Study Group. Curr. Chemother. **2**, 1331 (1978)
19. Krivit, W., Chilcote, R., Kyesmany, A., Sather, H., Anderson, J., Hammond, D.: Vindesine – Phase III. In: Proceedings of the First International Workshop on Vindesine, July 7, 1978. Stuttgart: Thieme (in press) (1979)
20. Loeb, E., Hill, J. M., Pardue, A. S., Khan, A., Hill, N. O., King, J. J., Hill, R.: Vindesine, a new vinca alkaloid in the treatment of leukemias and lymphomas. Curr. Chemother. **2**, 1334 (1978)
21. Mathé, G.: Experiences with vindesine at Villejuif. In: Proceedings of the First International Workshop on Vindesine, July 7, 1978. Stuttgart: Thieme (in press) (1979)
22. Mathé, G., Misset, J. L., De Vassal, F., Hayat, M., Machover, D., Bel Pomme, D., Schwarzenberg, L., Ribaud, P., Musset, H., Jasmin, C.: Phase-II clinical trial with vindesine for remission induction in acute leukemia, blastic crisis of myeloid leukemia, lymphosarcoma, and Hodgkin's disease. Absence of cross-resistance with vincristine. Med. Oncol. **3**, S21 (Abstract 51) (1977)
23. Mathé, G., Misset, J. L., De Vassal, F., Hayat, M., Machover, D., Bel Pomme, D., Schwarzenberg, L., Ribaud, P., Musset, M., Jasmin, C.: Phase-II clinical trial with vindesine for remission induction in acute leukemia, blastic crisis of chronic myeloid leukemia, lymphosarcoma, and Hodgkin's disease. Absence of cross-resistance with vincristine. Cancer Treat. Rep. **62**, 805 (1978)
24. Nelson, R. L., Dyke, R. W.: Phase I-II clinical investigation of vindesine (desacetyl vinblastine amide sulfate). Curr. Chemother. **2**, 1328 (1978)
25. Nelson, R. L., Root, M. A., Dyke, R. W., Ahmadzai, S.: Pharmacokinetics of desacetyl vinblastine amide (vindesine) in man. Proc. Am. Assoc. Cancer Res. **17**, 30 (1976)
26. Obrist, R., Paravicini, U., Hartmann, D., Nagel, G., Obrecht, J. P.: Vindesine – A clinical trial with special reference to neurological side effects. In: Proceedings of the International Workshop of Vindesine, July 7, 1978. Stuttgart: Thieme (in press) (1979)
27. Ochs, S., Worth, R.: Comparison of the block of fast axoplasmic transport in mammalian nerve by vincristine, vinblastine and desacetyl vinblastine amide sulfate (DVA)Am. Assoc. Cancer Res. **16**, (Abstracts no. 278 and 70) (1975)
28. Olmsted, J. B., Borisy, G. G.: Microtubules. Ann. Rev. Biochem. **42**, 507 (1973)
29. Owellen, R. J.: The pharmacokinetics of aromatic ring $^{3}$H-vinblastine in humans. Fed. Proc. **34**, 808 (1975)
30. Owellen, R. J., Donigian, D. W., Hartke, C. A., Dickerson, R. M., Kuhar, M. J.: The binding of vinblastine to tubulin and to particulate fractions of mammalian brain. Cancer Res. **34**, 3180 (1974)
31. Owellen, R. J., Hartke, C. A., Dickerson, R. M., Hains, F. O.: Inhibition of tubulin-microtubule polymerization by drugs of the vinca alkaloid class. Cancer Res. **36**, 1499 (1976)
32. Powles, T., Smith, I.: Vindesine in the treatment of breast cancer. In: Proceedings of the First International Workshop of Vindesine, July 7, 1978. Stuttgart: Thieme (in press) (1979)
33. Retsas, S., Newton, K. A., Westbury, G.: Vindesine as a single agent in the treatment of advanced malignant melanoma. In: Proceedings of the First International Workshop of Vindesine, July 7, 1978. Stuttgart: Thieme (in press) (1979)
34. Root, M. A., Gerzon, K., Dyke, R. W.: A radioimmunoassay for vinblastine and vincristine. Federation of Analytical Chemistry and Spectroscopy Societies, p. 125, Indianapolis, Indiana (1975)
35. Rosenthal, S., Kaufman, S.: Vincristine neurotoxicity. Ann. Intern. Med. **80**, 733 (1974)
36. Smith, I. E., Hedley, D. W., Powles, T. J., McElwain, T. J.: Vindesine in the treatment of breast carcinoma, malignant melanoma and other solid tumors. Paper presented at the Sixth Vinca alkaloid symposion, London, October 20, 1978
37. Soifer, D. (ed.): New York Academy of Science Conference on the Biology of Cytoplasmic Microtubules. Ann. NY Acad. Sci. **253**, 1 (1975)
38. Sweeney, M. J., Cullinan, G. J., Poore, G. A., Gerzon, K.: Experimental antitumor activity of vinblastine amides. Proc. Am. Assoc. Cancer Res. **15**, 37 (1974)
39. Tan, C.: Clinical and pharmacokinetic studies of vindesine in 50 children with malignant diseases. Curr. Chemother. **2**, 1326 (1978)
40. Todd, G. C., Gibson, W. R., Griffing, W. J., Morton, D. M.: The preclinical study of desacetyl vinblastine amide. Proc. Am. Assoc. Cancer Res. **16**, 70 (1975)
41. Todd, G. C., Gibson, W. R., Morton, D. M.: Toxicology of vindesine (desacetyl vinblastine amide) in mice, rats, and dogs. J. Toxicol. Environ. Health **1**, 843 (1976)
42. Weiss, H. D., Walker, M. D., Wiernik, P. H.: Neurotoxicity of commonly used antineoplastic agents. N. Engl. J. Med. **291**, 75 (1974)
43. Wilson, L.: Microtubules as drug receptors: Pharmacological properties of microtubules protein. Ann. NY Acad. Sci. **253**, 213 (1975)
44. Young, Ch.: Phase II evaluation of vindesine in patients with advanced cancer. Paper presented at the Sixth Vinca Alkaloid Symposium, London, October 20, 1978

Received November 22, 1978