Cancer Chemother Pharmacol (1982) 7:73–80

Cancer Chemotherapy and Pharmacology

Review

The Podophyllotoxin Derivatives VP16-213 and VM26

Brian F. Issell

Bristol Laboratories and State University of New York, Upstate Medical Center, P.O. Box 657, New York 13201, USA

Summary. *VP16-213 and VM26 are compounds with definite anticancer activity in specific tumor types. Despite 10 years of clinical development the full impact of these compounds in current cancer therapy requires further study.*

There is no conclusive evidence that one compound is superior to the other in any specific tumor type. The composite activities suggest possible differences in certain cancers such as small cell anaplastic lung cancer, lymphoma, leukemia, bladder and ovarian cancer, but sufficiently adequate studies to determine this have not been reported for any tumor.

Understanding the basic pharmacology of these compounds should also be considered of high priority since it is obvious that there is much to learn in this area and further clarification should allow improved clinical utilization. It is hoped that the presentations and discussions of the First International Symposium will generate a new wave of interest in future podophyllotoxin research and development.

Introduction and History

VP16-213 (etoposide) and VM26 (teniposide) are both semisynthetic derivatives of podophyllotoxin, a natural extract from certain plants of the genus Podophyllum. The aqueous extracts of the roots or rhizomes of these plants were termed podophyllin and were used hundreds of years ago as cathartics and anthelmintics by the American Indians and natives of the Himalayan mountain area independently. The American colonists subsequently used podophyllin as an emetic, and it was included in the first U.S. Pharmacopoeia (U.S.P. 1820).

The antimitotic properties of podophyllin were first demonstrated in 1946 and a chemical analysis of podophyllin revealed a number of compounds including podophyllotoxin. These natural products, however, were unacceptable for human use because of excessive toxicity. Sandoz in 1963 started a semisynthetic podophyllin derivative program. The two most successful anticancer compounds discovered from this program were VP16-213 and VM26. Both compounds have been undergoing clinical evaluation since 1971. It is, therefore, timely to now hold an international symposium on the podophyllotoxins so that a review may be made of their role in cancer patient management following 10 years of clinical investigation. Since the compounds differ chemically by only a small molecular substitution, this review will examine whether this difference is reflected in any significant difference in clinical profile.

Chemistry and Formulation

The chemical structures of VP16-213 and VM26 are shown in Fig. 1. They differ only by the substitution

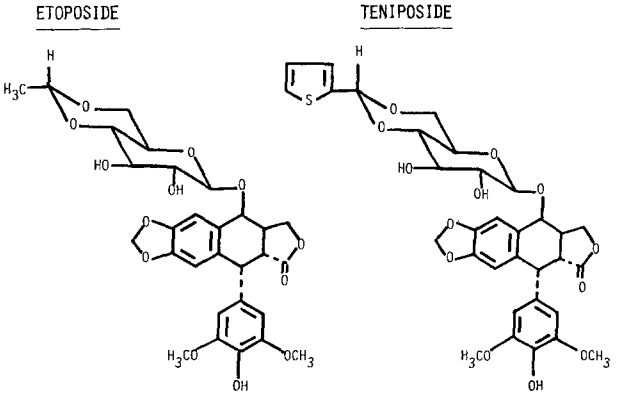

Fig. 1. Structural formulae of the podophyllotoxin derivatives etoposide (VP16) and teniposide (VM26)

0344-5704/82/0007/0073/$01.60

of a methyl group on the glucopyranoside by a thenylidine group.

Both compounds are poorly soluble in water and are supplied for clinical use in non-aqueous parenteral formulations for intravenous administration. VP16-213 is also supplied in gelatin capsules for oral administration.

VP16-213 is supplied in 5 ml ampules at a concentration of 20 mg/ml while each 5 ml ampule of VM26 has a concentration of 10 mg/ml. The intact ampules of both compounds are chemically stable for 4 years at room temperature from the date of manufacture. The dilution of one ampule of either VP16-213 or VM26 with 250 ml of isotonic sodium chloride or 5% dextrose in water gives a final concentration of 0.4 mg/ml for VP16-213 and 0.2 mg/ml for VM26. These dilutions are stable at room temperature and in ambient light for 6 h [9]. Increasing the drug concentration results in reduced stability. VP16-213 for oral administration is supplied in 10 mg and 50 mg gelatin capsule formulations in which the solid drug is finely dispersed in a wax-oil vehicle. Oral VP16-213 is usually administered at twice the intravenous dose [12].

Mechanism of Action

Both drugs have been labeled mitotic inhibitors because of metaphase arrest effects observed immediately following their addition to chick fibroblast tissue cultures. However, subsequent effects following drug exposure suggested that these compounds act in the cell cycle at or before the initiation of mitosis and differentiate them from the classical mitotic inhibitors [76, 77]. Also supporting their difference from classical spindle poisons is the observation that both VP16-213 and VM26 do not interfere with microtubular assembly [48].

An interesting observation is that VP16-213 produces DNA strand breakage when incubated with intact HeLa cells but has no DNA breakage effect on purified DNA [49]. These data encourage speculation that the DNA breakage effect may be caused by an indirect mechanism such as endonuclease activation, or alternatively that some type of intracellular activation is necessary to produce this effect.

Cytofluorometric studies have demonstrated that these compounds are cell cycle dependent and phase specific. In studies using human lymphoblastoid cell lines, the major delay of cell progression and maximum cell killing occurred in the S and G_2 phases [23, 46].

Clinical Potency, Dosage and Pharmacokinetics

The initial Phase 1 studies suggested that VM26 had twice the potency of VP16-213 when given daily for 5 consecutive days every 3 weeks and possibly 3 times the potency when administered on a weekly schedule. A VM26 dosage of 30 mg/m^2/day, day 1–5, appeared equivalent to VP16-213 at 60 mg/m^2/day by the same schedule [28, 29] and a weekly dose of 290 mg/m^2 VP16-213 seemed equivalent to a 90 mg/m^2 weekly dose of VM26 [2]. Subsequent studies suggest that the clinical potencies may not be this different and both drugs have been well tolerated at considerably higher dosage.

As a single agent, VP16-213 is commonly given at a dose of 300–600 mg/m^2 i.v. divided over 3 or 5 days and repeated every 3–4 weeks. VM26 monotherapy is commonly used in children at a dose of 150–200 mg/m^2 weekly or 100 mg/m^2 twice weekly. It has also been given to adults on an every 3–4 weekly schedule like VP16-213 but at a lower dose of 300 mg/m^2 divided over 5 days. Since the dose limiting toxicity of both drugs is myelosuppression, patients who may have bone marrow function compromised by prior radiotherapy or chemotherapy should have therapy initiated in the lower dose range. Subsequent doses of therapy should be modulated according to peripheral blood counts for all patients.

Pharmacokinetic studies showed that VP16-213 had a 3 times greater theoretical plasma clearance and a 6 times greater renal clearance than VM26; and this may, in part, explain observed potency differences [2]. In adults using radiolabeled compounds, the terminal half-life for VP16-213 varied between 6.6 and 15.8 h [18], while that of VM26 varied from 11 to 38.5 h [19]. No observed CSF penetration differences were found with CSF concentrations generally below 10% of concurrent plasma concentrations for most patients.

Plasma samples from children using a high pressure liquid chromatography assay showed the mean terminal half-life of VP16-213 to be 5.7 h and that of VM26 to 9.8 h [31].

Clinical Single Agent Activity

The composite response rates for VP16-213 and VM26 single agent therapy are shown in Table 1. When considering these responses, one should be aware that they are compiled from studies utilizing various doses and schedules all of which may not have been optimal. Furthermore, the proportion of patients who had been heavily pretreated or who had poor performance status is unknown for each tumor type.

Table 1. Composite activity of VP16-213, VM26 monotherapy according to tumor type

Tumor type	VP16-213			VM26		
	No. Evaluable patients	% Responders	References	No. Evaluable patients	% Responders	References
Lung						
Small cell	262	40 (6CR)	[3, 12, 16, 25, 32, 37, 44, 57, 78, 80, 82]	38	21 (5CR)	[67, 75, 85]
Non-small cell	113	6	[26, 32, 57]	58	3	[7, 67, 75]
Testis	87	26 (3CR)	[10, 29, 33, 57]	6	0	[21, 28]
Lymphoma						
Histiocytic	104	38 (1CR)	[5, 13, 29, 32, 42, 51]	84	40	[15, 21, 28, 51, 74, 79]
Lymphocytic	31	10	[13, 29, 51]	58	41	[15, 28, 51, 74]
Mycosis fungoides	6	33	[41, 54]	0	–	–
Hodgkin's disease	55	18	[13, 29, 51, 57]	101	33	[15, 21, 28, 51, 74, 79]
Acute leukemia						
Lymphocytic	44	7	[29, 47, 51, 62]	44	18 (2CR)	[8, 66]
Non-lymphocytic	170	26 (12CR)	[6, 11, 29, 51, 62, 73]	14	7	[8, 62]
Myelomonocytic	42	46 (36CR)	[6, 29, 51, 52, 73]	0	–	–
Neuroblastoma	11	27 (9CR)	[14, 57]	38	34	[8, 65]
Breast	294	8	[1, 24, 29, 32, 57, 69, 81]	11	36	[75]
Brain	5	0	[29, 57]	63	29	[34, 45. 71, 75]
Bladder	33	3	[20, 29, 32, 57]	86	31	[53, 58]
Ovary	69	4	[27, 29, 30, 32, 44, 50, 57, 72]	28	32 (4CR)	[21, 43, 75, 85]
Cervix	31	0	[72]	0	–	–
Uterus	9	22	[57]	0	–	–
Colorectum	171	5	[22, 29, 32, 56, 59]	20	10	[21, 75]
Hepatoma	6	50	[11]	0	–	–
Melanoma	76	1	[13, 32, 55, 56]	21	0	[4]
Head and neck	56	2	[29, 57]	16	0	[28]
Soft tissue sarcoma	29	3	[13, 28, 55, 57]	16	0	[84]
Ewing's sarcoma	3	33	[14]	0	–	–
Wilm's tumor	6	33	[14]	0	–	–
Rhabdomyosarcoma	7	43	[14, 57]	0	–	–
Osteosarcoma	5	0	[57]	0	–	–
Kidney	52	2 (2CR)	[36, 57]	12	0	[39]
Prostate	9	11	[44, 57]	0	–	–
Gastric	19	10	[20, 28, 55, 56]	6	0	[21]
Esophagus	9	2	[56]	15	0	[21]
Mesothelioma	7	0	[32, 55, 56]	0	–	–
Thyroid	Single case report response		[60]	0	–	–

Responders = Patients with ≥ 50% measured tumor regression
CR = Complete response

Lung Cancer

VP16-213 is probably one of the most active single agents in small cell lung cancer with a composite single agent response rate (> 50% measured tumor regression) of 40% in 262 patients. This includes a 6% complete response rate. Although earlier reports suggested excellent activity for VP16-213 in patients who had failed front-line therapy [16, 80], recent results in patients refractory to the aggressive front-line combination therapy currently used are not as encouraging [78]. Activity appears to be schedule-dependent

with multiple dosage over 3 or 5 days showing superiority over single-dose administration [40]. VP16-213 is effective when administered orally at approximately twice the intravenous dose [12]. VM26 has not been adequately studied in small cell lung cancer, but the Ludwig Institute in Sydney found a 28% response rate including 8% complete responses in 25 patients [85]. There are no data demonstrating schedule or oral absorption differences between VP16-213 and VM26.

Testicular Cancer

VP16-213 appears active in testicular cancer patients refractory to front-line combination chemotherapy. Response rates up to 46% have been reported. Although the partial responses are usually of relatively short duration, complete responses of greater than 1 year's duration have been reported from the Royal Marsden Hospital in England [33]. VM26 has not been adequately tested in this situation.

Malignant Lymphoma

As suggested by the early phase 1 studies, both VP16-213 and VM26 are active in Hodgkin's disease and other malignant lymphomas. The results of VP16-213 in diffuse histiocytic lymphoma have been especially encouraging. Bender et al. noted a 42% response rate in 19 evaluable patients who had become refractory to front-line combination chemotherapy [5].

Leukemia

VP16-213 does appear to have activity in adult acute myelogenous leukemia with 4 of 12 complete remissions reported in the early EORTC experience [29], 7 of 20 reported by Mathé et al. [51], and 2 of 20 from the Royal Marsden Hospital experience [73]. Of special interest is the response rate for patients with myelomonocytic and monocytic leukemia, and it has been suggested that this compound may have a specific role in acute leukemia where monocytoid cells have failed to clear with conventional first-line therapy [6].

VM26 appares to have an important role in the management of pediatric acute lymphoblastic leukemia (A.L.L.). Studies undertaken at St. Jude Children's Hospital demonstrated the activity of VM26 as a single-agent in refractory A.L.L. [62]. However, its major contribution appears to be in combination with cytarabine (ara. C) in this situation (videi infra). VP16-213 also appears to have activity as a single agent in refractory A.M.L. in the St. Jude Children's Hospital experience [62]. Whether any difference in activity exists between the two compounds when they are given at maximum tolerated dosage has not been adequately tested.

Neuroblastoma

VM26 has meaningful activity in pediatric refractory neuroblastoma. Both St. Jude Children's Hospital and the Children's Cancer Study Group (CCSG) found that 3 of 7 patients and 10 of 31 patients, respectively, responded [8, 65]. VP16-213 also appears active in this disease. The CCSG found one response in seven evaluable patients [14], and the Cancer and Leukemia Group B reported 2 responses in 4 patients [57].

Brain Tumors

VM-26 does appear to have activity in brain tumors. Tumor response as evidenced by objective tumor regression and neurological improvement have been reported by Sklansky et al. in 2 of 4 patients [71]. Spremulli et al. also reported that 2 of 10 patients with malignant glioma achieved evaluable partial responses to VM26 therapy [75], and Gerosa et al. reported partial and complete responses in 35% of 20 evaluable patients [34]. Responses were seen in patients who were progressing on nitrosoureas. VP16-213 has not been adequately tested in brain tumors.

Breast Cancer

The earlier composite data suggested that VP16-213 did not have useful activity in refractory breast cancer. However, Schell et al. at M. D. Anderson Hospital in Houston, Texas, USA, have recently reported useful partial responses in 9 of 52 heavily pretreated patients [69]. These results suggest that the role of VP16-213 in this disease should be further explored. VM26 has not yet been adequately tested in breast cancer.

Clinical Combination Therapy

It is not always possible to evaluate the contribution of VP16-213 or VM26 in the many combination therapy studies. Both compounds are easily combined with other drugs because of their good tolerance and share with many other cytotoxic agents the dose-limiting toxicity of myelosuppression. Unfortunately, this has often resulted in VP16-213 or VM26 being added in

Table 2. Etoposide (VP16-213) – teniposide (VM26) clinical toxicities

VP16-213	VM26
Myelosuppression	
Leukopenia dose limiting and predictable	Same
Thrombocytopenia less frequent	
Gastrointestinal	
Nausea, vomiting, and infrequent diarrhea	Same
Anorexia	
Stomatitis uncommon	
Alopecia	
Common and reversible	Same
Acute	
Uncommon and include fever, chills, hypotension and bronchospasm	Same
Hypotension may be relieved by increasing infusion time	
Peripheral neuropathy	
Mild and infrequent	Same
More serious and frequent when given with vinca alkaloids	
Pulmonary	
Not reported	1 Case hyaline membrane disease

suboptimal dosage so that their full potential impact is uncertain. Nonetheless, some interesting therapeutic effects have been observed when the podophyllotoxins have been added to specific cytotoxic compounds.

Therapeutic synergy between the podophyllotoxins and cisplatin has been observed in P388 cancer-bearing mice [68]. The synergy between VP16-213 and cisplatin has been explored in patients with small cell lung cancer [70], non-small cell lung cancer [35], and refractory testicular cancer [83], with encouraging results. The combination of cisplatin with VM26 also appears useful in refractory neuroblastoma [38].

Of special interest is the reported therapeutic synergism between VM26 and cytarabine (ara C) in refractory pediatric A.L.L. Rivera et al. [63] had initially shown a synergy between these two compounds in L1210 inoculated mice. Following this observation, clinical studies were initiated. Nine of 33 children with A.L.L. in relapse achieved complete remissions in one study [61]. In a subsequent study, the combination resulted in 9 of 14 patients achieving complete remissions after they had failed remission induction with standard therapy. Six of these patients had also been treated with prior cytarabine [64].

Clinical Toxicities

The clinical toxicities are listed in Table 2. The toxicity profiles for both compounds are similar. Both compounds are well tolerated and easily managed in the clinic with predictable myelosuppression (mainly leukopenia) being the dose-limiting effect. Other less comon toxicities are gastrointestinal, acute hypersensitivity reactions and peripheral neuropathy. A case of hyaline membrane pulmonary toxicity associated with VM26 administration has recently been reported [17].

Conclusions

Both VP16-213 and VM26 appear to be useful compounds in the management of certain tumors. Although they differ somewhat in their pharmacokinetic profiles, there is no evidence that one drug is superior to the other in a specific tumor type. Their clinical toxicities are similar as well. The papers presented at this First International Symposium will further outline the established and future potential roles for these agents. Of special interest is the addition of these drugs into successful combination regimens.

Acknowledgements. I am grateful to Robert L. Comis, M.D., for his critical review of this manuscript and to Ms. Judi Brinck for manuscript preparation.

References

1. Ahmann DL, Bisel HF, Eagan RT, Edmonson JH, Hahn RG, O'Connell MJ, Frytak S (1976) Phase II evaluation of VP16-213 (NSC-141540) and cytembena (NSC-104801) in patients with advanced breast cancer. Cancer Treat Rep 60: 633
2. Allen LM, Creaven PJ (1975) Comparison of the human pharmacokinetics of VM26 and VP16, two antineoplastic epipodophyllotoxin glucopyranoside derivatives. Eur J Cancer 11: 697

3. Anderson G, Bowyer F, Williams L (1981) The treatment of advanced bronchogenic carcinoma with monoagent oral VP16-213. Thorax (in press)
4. Bellet RE, Catalano RB, Mastrangelo MJ, Berd D, Koons LS (1978) Phase II trial of VM26 in patients with metastatic malignant melanoma. Cancer Treat Rep 62: 445
5. Bender RA, Anderson T, Fisher RT, Young RC (1978) The activity of the epipodophyllotoxin VP16 in the treatment of combination chemotherapy resistant non-Hodgkin's lymphoma. Am J Hematol 5: 203
6. Bernasconi C, Lazzarino M, Morra E (1976) The use of an epipodophyllotoxin derivative (VP16-213) in the treatment of acute monocytic and myelomonocytic leukemias. In: Stacher A, Hocker P (Hrsg) Erkrankungen der Myelopoese-Leukämien, myeloproliferatives Syndrom, Polyzythämie. Urban and Schwarzenberg, München Berlin, S 224
7. Bhuchar VK, Boyle LE, Lanzotti VJ (1978) VM26 in non-oat cell bronchogenic carcinoma. Proc ASCO 19: 407
8. Bleyer WA, Krivit W, Chard RL, Jr, Hammond D (1979) Phase II study of VM26 in acute leukemia, neuroblastoma, and other refractory childhood malignancies: A report from the children's cancer study group. Cancer Treat Rep 63: 977
9. Bristol Laboratories' Product Development Research Reports (1980)
10. Cavalli F, Klepp O, Renard J, Rohrt M, Alberto P (1981) A phase II study of oral VP16-213 in non-seminomatous testicular cancer. Eur J Cancer 17: 245
11. Cavalli F, Sonntag RW, Brunner KW (1977) Epipodophyllotoxin VP16-213 in acute non-lymphoblastic leukemia. Lancet 1: 362
12. Cavalli F, Sonntag RW, Jungi F, Senn H, Brunner KW (1978) VP16-213 monotherapy for remission induction of small cell lung cancer – A randomized trial using three dosage schedules. Cancer Treat Rep 62: 473
13. Cecil JW, Quagliana JM, Coltman CA, Al-Sarraf M, Thigpen T, Groppe W (1978) Evaluation of VP16-213 in malignant lymphoma and melanoma. Cancer Treat Rep 62: 801
14. Chard RL, Krivit W, Bleyer WA, Hammon D (1979) Phase II study of VP16-213 in childhood malignant disease. Cancer Treat Rep 63: 1755
15. Chiuten DF, Bennett JM, Creech RH, Glick J, Falkson G, Brodovsky HS, Begg CG, Muggia FM, Carbone PO (1979) VM26, a new anticancer drug with effectiveness in malignant lymphoma: An eastern cooperative oncology group study (EST 1474). Cancer Treat Rep 63: 7
16. Cohen MH, Broder LE, Fossieck BE, Ihde DC, Minna JD (1977) Phase II clinical trial of weekly administration of VP16-213 in small cell bronchogenic carcinoma. Cancer Treat Rep 61: 489
17. Commers JR, Foley JF (1979) Pulmonary hyaline membrane disease occurring in the course of VM26 therapy. Cancer Treat Rep 63: 2093
18. Creaven PJ, Allen LM (1975a) EPEG, a new antineoplastic epipodophyllotoxin. Clin Pharmacol Ther 18: 221
19. Creaven PJ, Allen LM (1975b) PTG, a new antineoplastic epipodophyllotoxin. Clin Pharmacol Ther 18: 227
20. Creaven PJ, Newman SJ, Selawry OS, Cohen MH, Primack A (1974) Phase I clinical trial of weekly administration of 4′demethyl-epipodophyllotoxin 9-(4,6-0-ethylidene-β-D-glycopyranoside) (NSC-141540; VP16-213). Cancer Chemother Rep 58: 901
21. Dombernowsky P, Nissen NI, Larsen V (1972) Clinical investigation of a new podophyllum derivative, epipodophyllotoxin, 4′-demethyl-9-(4,6-0-2-thenylidene-β-D-glucopyranoside) NSC-122819), in patients with malignant lymphomas and solid tumors. Cancer Chemother Rep 56: 71
22. Douglass HO, Jr, McIntyre JM, Evans JT, Kaufman J, Carbone PP (1977) Methyl CCNU (meCCNU) plus β-2′-deoxythioguanosine vs. VP16 or diglycoaldehyde (DGA) in advanced, previously treated colorectal adenocarcinoma: A phase II study of the ECOG. Proc Am Assoc Cancer Res 18: 313
23. Drewinko B, Barlogie B (1976) Survival and cycle-progression delay of human lymphoma cells in vitro exposed to VP16-213. Cancer Treat Rep 60: 1295
24. Eagan RT, Ahmann DL, Bisel HF (1976) Evaluation of VP16 and the combination of adriamycin and vincristine in advanced breast cancer. Oncology 33: 146
25. Eagan RT, Carr DT, Frytak S, Rubin J, Lee RE (1976) VP16-213 versus polychemotherapy in patients with advanced small cell lung cancer. Cancer Treat Rep 60: 949
26. Eagan RT, Ingle JN, Creagan S, Frytak S, Kvels LK, Rubin J, McMahon RT (1978) VP16-213 chemotherapy for advanced squamous cell carcinoma and adenocarcinoma of the lung. Cancer Treat Rep 62: 843
27. Edmonson JH, Decker DG, Malkasian GD, Webb MJ, Jorgensen EO (1978) Phase II evaluation of VP16-213 (NSC-141540) in patients with advanced ovarian carcinoma resistant to alkylating agents. Gynecol Oncol 6: 7
28. European organization for research on the treatment of cancer. Cooperative group for leukemias and haematosarcomas (1972) Clinical screening of epipodophyllotoxin VM26 in malignant lymphomas and solid tumours. Br Med J 2: 744
29. European organization for research on the treatment of cancer, clinical screening group (1973) Epipodophyllotoxin VP16-213 in treatment of acute leukaemias, haematosarcomas and solid tumours. Br Med J 3: 199
30. European organization for research on the treatment of cancer, ovarian group (1979) Phase II treatment of oral VP16 in treatment of advanced ovarian cancer. Proc 5th Med Oncol Soc Meeting, Nice, p 5
31. Evans WE, Sinkule JA, Horvath A, Crom WR, Dow LW, Rivera G (1981) Clinical pharmacology of VM26 (NSC 122829) and VP16 (NSC141540) children with cancer. Proc Am Assoc Cancer Res 22: 174
32. Falkson G, VanDyk JJ, VanEden EB, VanDerBergh JA, Falkson H (1975) A clinical trial of the oral form of 4′-demethyl-epipodophyllotoxin-β-1-D ethylidene glucoside (NSC 141540) VP16-213. Cancer 35: 1141
33. Fitzharris BM, Kaye SB, Saverymuttu S, Newlands ES, Barrett A, Peckham MJ, McElwain TJ (1980) VP16-213 as a single agent in advanced testicular tumors. Eur J Cancer 16: 1193
34. Gerosa MS, DiStefano E, Olivi A (1981) VM26 monochemotherapy trial in the treatment of recurrent supratentorial gliomas: preliminary report. Surg Neurol 15: 128
35. Goldhirsch A, Joss RA, Cavalli F, Sonntag RW, Brunner KW (1981) Cis-dichlorodiammineplatinum (II) and VP16-213 combination chemotherapy for non-small cell lung cancer. Med Pediatr Oncol 9: 205
36. Hahn RG, Bauer M, Walter J, Creech R, Bennet J, Wampler G (1979) Phase II study of single-agent therapy with megestrol acetate, VP16-213, cyclophosphamide, and dianhydrogalacitol in advanced renal cell cancer. Cancer Treat Rep 63: 513
37. Hansen M, Hirsch F, Dombernowsky P, Hansen HH (1977) Treatment of small cell anaplastic carcinoma of the lung with the oral solution of VP16-213. Cancer 40: 633
38. Hayes FA, Green A, Casper J, Cornet J, Evans W (1981) Clinical evaluation of sequentially scheduled cisplatin and VM26 in neuroblastoma: response and toxicity. Cancer (in press)
39. Hire EA, Samson MK, Fraile RJ, Baker LH (1979) Use of VM26 as a single agent in the treatment of renal carcinoma. Cancer Clin Trials 2: 293
40. Issell BF, Crooke ST (1978) Etoposide (VP16-213). Cancer Treat Rev 6: 107

41. Jacobs P, King HS, Gordon W (1975) Chemotherapy of mycosis fungoides. Letter to the editor. S. Afr Med J 49: 1268
42. Jacobs P, King HS, Sealy GRH (1975) Epipodophyllotoxin (VP16-213) in the treatment of diffuse histiocytic lymphomas. S Afr Med J 49: 483
43. Jankowski RP, Vahrson H (1977) The toxicity of massive doses of VM26 (4-demethyl-epipodophyllotoxin-β-D-thenylidene glucoside). A contribution to the therapy of advanced ovarian cancer. Med Klin 72: 2122
44. Jungi WF, Senn HJ (1975) Clinical study of the new podophyllotoxin derivative, 4′-demethyl-epipodophyllotoxin 9-(4,6-0-ethylidene-β-D-glucopyranoside) (NSC-141540; VP16-213), in solid tumors in man. Cancer Chemother Rep 59: 737
45. Kessinger A, Lemon HM, Foley JF (1979) VM26 as a second drug in the treatment of brain gliomas. Cancer Treat Rep 63: 511
46. Krishan A, Packa K, Frei E (1975) Cytofluorometric studies on the action of podophyllotoxin and epipodophyllotoxins (VM26, VP16-213) on the cell cycle traverse of human lymphoblast. J Cell Biol 66: 521
47. Lau ME, Hansen HH, Nisser HH, Pederson H (1979) Phase I trial of a new form of an oral administration of VP16-213. Cancer Treat Rep 63: 485
48. Locke JD, Horwitz SB (1976a) Effects of VP16-213 on microtubule assembly in vitro and nucleoside transport in HeLa cells. Biochemistry 15: 5435
49. Locke JD, Horwitz SB (1976b) Effect of VP16-213 on the intracellular degradation of DNA in HeLa cells. Biochemistry 15: 5443
50. Maskens AP, Armand JP, Lacave AJ, DeJager RL, Hansen HH, Wolff JPM (1981) Phase II clinical trial of VP16-213 in ovarian cancer. Cancer Treat Rep 65: 329
51. Mathé G, Schwarzenberg L, Pouillart P, Oldham R, Weiner R, Jasmin C, Rosenfeld C, Hayat M, Misset JL, Musset M, Schneider M, Amiel JL, DeVassal F (1974) Two epipodophyllotoxin derivatives, VM26 and VP16-213, in the treatment of leukemias, hematosarcomas, and lymphomas. Cancer 34: 985
52. McKenna RW, Bloomfield CD, Dick F, Nesbit ME, Brunning RD (1975) Acute monoblastic leukemia diagnosis and treatment of ten cases. Blood 46: 481
53. Mechl Z, Rovny F, Sopkova B (1977) VM26 (4-demethyl-epipodophyllotoxin-β-D-thenylidine glucoside) in the treatment of urinary bladder tumors. Neoplasma 24: 411
54. Molin L, Thomsen K, Volden G, Bergquist-Karlsson A, Hallberg O, Hellbe L (1978) Epipodophyllotoxin (VP16-213) in mycosis fungoides: A report from the scandinavian mycosis fungoides study group. Acta Derm Venereol (Stockh) 49: 84
55. Nissen NI, Dombernowsky P, Hansen HH, Larsen V (1976) Phase I clinical trial of an oral solution of VP16-213. Cancer Treat Rep 60: 943
56. Nissen NI, Larsen V, Pedersen H, Thomson K (1972) Phase I clinical trial of a new antitumor agent, 4′-demethylepipodophyllotoxin 9-(4-6-0-ethylidene-β-D-glucopyranoside) (NSC-141540; VP16-213). Cancer Chemother Rep 56: 769
57. Nissen NI, Pajak TF, Leone LA, Bloomfield CD, Kennedy BJ, Ellison RR, Silver RT, Weiss RB, Cuttner J, Falkson G, Kung F, Bergevin PR, Holland JF (1980) Clinical trial of VP16-213 (NSC 141540) i.v. twice weekly in advanced neoplastic disease a study by the cancer and leukemia group B. Cancer 45: 232
58. Pavone-Macaluso M, EORTC Genito-urinary Tract Co-operative Group A (1976) Single-drug chemotherapy of bladder cancer with adriamycin, VM26, or bleomycin. Eur Urol 2: 138
59. Perry MC, Moertel CG, Schutt AJ, Reitemeier RJ, Hahn RG (1976) Phase II studies of dianhydrogalactitol and VP16-213 in colorectal cancer. Cancer Treat Rep 60: 1247
60. Reyes J, Shimaoka K (1975) Chemotherapy of thyroid carcinoma. Proc ASCO 16: 229
61. Rivera G, Aur RJ, Dahl GV, Pratt CB, Wood A, Avery TL (1980) Combined VM26 and cytosine arabinoside in treatment of refractory childhood lymphocytic leukemia. Cancer 45: 1284
62. Rivera G, Avery T, Pratt C (1975) 4′-demethylepipodophyllotoxin 9-(4,6-0-2-thenylidene-β-D-glucopyranoside) (NSC-122819; VM26) and 4′-demethylepipodophyllotoxin 9-(4,6-0-ethylidene-β-D-glucopyranoside) (NSC-141540; VP16-213) in childhood cancer: preliminary observations. Cancer Chemother Rep 59: 743
63. Rivera G, Avery T, Robert D (1975) Response of L1210 to combinations of cytosine arabinoside and VM26 or VP16-213. Eur J Cancer 11: 639
64. Rivera G, Dahl GV, Bowman WP, Avery TL, Wood A, Aur RJ (1980) VM26 and cytosine arabinoside combination chemotherapy for initial induction failures in childhood lymphocytic leukemia. Cancer 46: 1727
65. Rivera G, Green A, Hayes A, Avery T, Pratt C (1977) Epipodophyllotoxin VM26 in the Treatment of Childhood Neuroblastoma. Cancer Treat Rep 61: 1243
66. Rosenstock JG, Donaldson MH (1976) Phase I–II trial of VM26 (NSC-122819) in the treatment of children with late-stage leukemia. Cancer Treat Rep 60: 265
67. Samson MK, Baker LH, Talley RW, Fraile RJ (1978) VM26 (NSC-122819): A clinical study in advanced cancer of the lung and ovary. Eur J Cancer 14: 1395
68. Schabel FM, Jr, Trader MW, Laster WR, Jr, Corbett TH, Griswold DP, Jr (1979) Cis-dichlorodiammineplatinum (II): combination chemotherapy and cross-resistance studies with tumors of mice. Cancer Treat Rep 63: 1459
69. Schell FC, Yap HY, Hortobagyi GN, Buzdar AU, Blumenschein GR, Issell BF, Esparza L (1981) Phase II study of VP16-213 (etoposide) in refractory metastatic breast cancer. Proc ASCO 2: 357
70. Sierocki JS, Hilaris BS, Hopfan S, Martini N, Barton D, Golbey RB, Wittes RE (1979) Cis-dichlorodiammineplatinum (II) and VP16-213: An active induction regimen for small cell carcinoma of the lung. Cancer Treat Rep 63: 1593
71. Sklansky BD, Mann-Kaplan RS, Reynolds AF, Rosenblum ML, Walker MD (1974) 4′-Demethyl-epipodophyllotoxin-β-D-thenylidene-glucoside (PTG) in the treatment of malignant intracranial neoplasms. Cancer 33: 460
72. Slayton RE, Creasman WT, Petty W, Bundy B, Blessing JA (1979) Phase II trial of VP16-213 in the treatment of advanced squamous cell carcinoma of the cervix and adenocarcinoma of the ovary. Cancer Treat Rep 63: 2089
73. Smith IR, Gerken ME, Clink HM, McElwain TJ (1976) VP16-213 in acute myelogenous leukaemia. Postgrad Med J 52: 66
74. Sonntag RW, Senn HJ, Nagel G, Giger K, Alberto P (1974) Experience with 4′-demethylepipodophyllotoxin 9-(4,6-0-2-thenylidene-β-D-glucopyranoside); VM26; NSC-122819 in the treatment of malignant lymphosis. Eur J Cancer 10: 93
75. Spremulli E, Schulz JJ, Speckhart VJ, Wampler GL (1980) Phase II study of VM26 in adult malignancies. Cancer Treat Rep 64: 147
76. Stahelin H (1970) 4′-Demethyl-epipodophyllotoxin thenylidene glucoside (VM26), a podophyllum compound with a new mechanism of action. Eur J Cancer 6: 303
77. Stahelin H (1973) Activity of new glycosidic lignan derivative (VP16-213) related to podophyllotoxin in experimental tumors. Eur J Cancer 9: 215
78. Tempero M, Kessinger A, Lemon HM (1981) VP16-213 therapy in patients with small cell carcinoma of the lung after failure on combination chemotherapy. Cancer Clin Trials 4: 155
79. Trempe G, Sykes M, Young C, Krakoff I (1970) Phase I trial of the podophyllotoxin derivative VM26. Proc Am Assoc Cancer Res 11: 79

80. Tucker RK, Ferguson A, VanWyk C, Sealy R, Hewitsen R, Levin W (1978) Chemotherapy of small cell carcinoma of the lung with VP16-213. Cancer 41: 1710
81. Vaughn CB, Panettiere F, Thigpen T, Bottomley R, Hoogstraten B, Samal B (1981) Phase II evaluation of VP16-213 in patients with advanced breast cancer: A southwest oncology group study. Cancer Treat Rep 65: 443
82. VonEyben F, Arwidi A, Mattsson W (1980) VP16-213 in small cell carcinoma of the lung. 2nd World Congress on Lung Cancer, Copenhagen, p 227
83. Williams SD, Einhorn LH, Greco FA, Oldham R, Fletcher R (1980) VP16-213 salvage therapy to refractory germinal neoplasms. Cancer 46: 2154
84. Wilson WW, Bull F, Solomon J (1976) Phase II study of VM26 in advanced non-lymphomatous sarcoma. Proc ASCO 17: 250
85. Woods RL, Fox RM, Tattersall MHN (1979) Treatment of small cell bronchogenic carcinomma with VM26. Cancer Treat Rep 63: 2011

Accepted July, 1981