Cancer Chemother. Pharmacol. 3, 71–80 (1979)

Cancer Chemotherapy and Pharmacology

General Review

Podophyllotoxin Derivative VP 16-213

A. M. Arnold

CRC Medical Oncology Unit, Level F, Centre Block, Southampton General Hospital, Southampton, England

Summary. *VP 16-213, a derivative of podophyllotoxin, is currently entering phase-III studies. Its mode of action is incompletely understood, but differs markedly from that of its parent compound. The greatest lethal damage is experienced by cells in the late S and G_2 phases. In the L 1210 system the drug shows marked schedule dependency: prolonged administration may be more effective than single bolus administration.*

As a single agent, VP 16-213 is the most active compound yet tested against small-cell bronchial carcinoma. It may also prove to be a useful agent in patients with other types of lung tumour, testicular teratomas, and some types of leukaemia. No long-term or cumulative toxicity has been reported. Most side effects are predictable and reproducible.

Podophyllin is the crude extract from the roots of two related plants, the American mandrake or May apple, *Podophyllum peltatum,* and *Podophyllum emodi* from India. It was first used by Kaplan [36] to treat condyloma acuminata, and later for other benign skin conditions. The main active constituent of podophyllin, podophyllotoxin, is known to produce metaphase arrest [14, 17, 39, 60] and to have a similar mode of action to the other spindle poisons, colchicine and the Vinca alkaloids. More recently it has been shown that podophyllotoxin binds competitively to the same site on the microtubular protein, tubulin, as does colchicine, and thus interferes with the assembly of microtubules in the mitotic apparatus [37, 42, 44, 65–67]. In addition to this effect on mitosis, podophyllotoxin inhibits a variety of other microtubule-dependent processes, including fast axioplasmic transport [53], long saltatory intracellular movements [29], and cilia regeneration [45]; at higher concentrations it has also been shown to inhibit nucleoside transport [48].

Reprint requests should be addressed to: A. M. Arnold

Podophyllotoxin itself is too toxic to be useful in man; however, two early derivatives, SPI (podophyllic acid ethyl hydrazide) and SPG (a mixture of purified benzylidene glucosides of *podophyllum emodi*) underwent limited clinical trials [12, 27, 62, 63]. Although some antitumour activity was demonstrated, these compounds were also found to be too toxic to warrant further development.

In an attempt to discover less toxic derivatives, Stähelin, at Sandoz laboratories, modified different positions on the podophyllotoxin ring system, which resulted in the synthesis of two semisynthetic glucoside derivatives, VM 26 [61] and VP 16-213 [59]. A comparative analysis of the two drugs has been carried out by Rozencweig et al. [55]: Both compounds are still undergoing investigation as antitumour agents, but are now entering phase-III studies. This review concentrates on the latter compound, VP 16-213, which is active in several tumours of man, and appears to be the most active single agent yet tested for the treatment of small-cell carcinoma of the bronchus (Table 2). It also appears to have a highly specific action on leukaemic monocytes.

Chemistry

VP 16-213 or 4′-demethyl-epipodophyllotoxin-9-(4, 6-0 ethylidene β-D glucopyranoside) (NSC 141540) differs from podophyllotoxin at three positions (Fig. 1). It has a glucoside moiety at the C-4 carbon, enantiomeric configuration of podophyllotoxin at the C-4 carbon atom, and a hydroxyl group at the C-4′ position [42]. Its synthesis has been fully described by Keller-Juslén [38]. The molecular weight of the compound is 588 and it is highly water-insoluble. It can only be solubilised by dissolving in either a detergent mixture of DMSO and Tween 80 or a mixture of polyethylene glycol 300, ethanol, and Tween 80. This gives an oily solution, which, when dissolved in physiological fluids and allowed to

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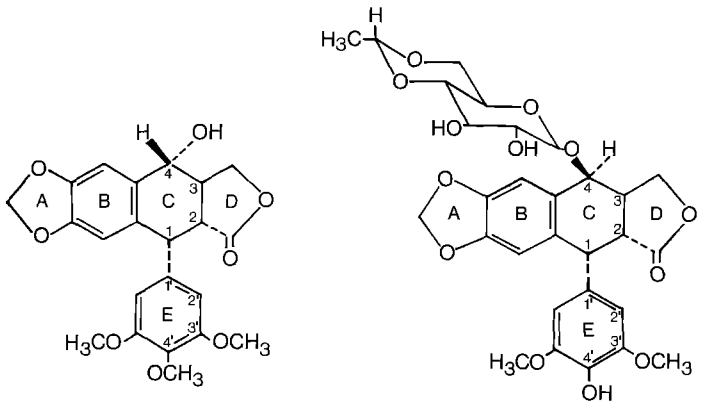

Podophyllotoxin

4'-Demethyl epipodophyllotoxin Ethylidene β-D-glucoside (VP-16-213)

Fig. 1. Structure formulas of podophyllotoxin (*left*) and V.P. 16-213 (*right*)

stand at room temperature, precipitates out after several hours. Dilution in sodium chloride results in the following solution stability before the precipitation usually occurs.

1 : 20 – 30 min,
1 : 50 – 3 h,
1 : 100 – 6 h.

Studies at Sandoz laboratories suggest that even when precipitation does not occur, the drug may be light-sensitive and unstable beyond 6 h in solution (personal communication).

In vitro Activity

In vitro activity has been shown against a number of cell lines [31, 34, 40, 47]. The earliest change noted against the P 815 murine mastocytoma is a marked and immediate decrease in mitotic index [31]. When the medium is supplemented by either 1 μg or 10 μg drug/ml, cell proliferation ceases after 1.5 h. At the higher concentration the total cell number drops below the initial value within 5–6 h. The ED_{50} (concentration necessary for 50% inhibition of multiplication) for the P 815 mastocytoma is 0.046 μg/ml [59]. Human tumour cells (HeLa) are less sensitive, the ED_{50} being 0.14 μg/ml. Thus, the drug appears to be about ten times less active in vitro than its congener VM 26 (ED_{50} for P 815 = 0.005 μg/ml) [58].

Chick fibroblast cells treated with VP 16-213 are transiently arrested in metaphase but this effect is superseded by either lysis of cells or inhibition of the beginning of mitosis [58]. At higher concentrations, cells preparing for mitosis are seen to disintegrate into small droplets. Huang et al. [34] studied the effect of treating four human haemopoietic cell lines with differing concentrations of VP 16-213. In all four lines they found a high incidence of multiple chromosomal abnormalities, the degree of which was related to dose and duration of drug exposure.

Animal Studies

The LD_{50} for mouse, rat, and rabbit following a single IV bolus is 118, 68, and 780 mg/kg, respectively [59]. The equitoxic doses for a 2-week period are smaller when the drug is given daily than when it is given twice weekly. For transplantable rodent solid tumours VP 16-213 shows activity against sarcomas 37 and 180 and the Walker carcinosarcoma. In this last tumour, a 30-min infusion appeared to be superior to either an IV bolus or oral administration. Activity has also been shown against the P 815, P 1534, and L 1210 leukaemias. Dombernowsky and Nissen [18] undertook a comparative study of various doseage schedules in mice with L 1210 leukaemia and noted marked schedule dependency. The percentage 'cure' rate rose to 100 when the drug was given in divided doses over 24 h. The same total dose given by a single injection only produced 58% cure. They also concluded that VP 16-213 was one of the most active drugs yet tested in the L 1210 system. Vietti et al. [63] used a spleen-colony assay technique to quantify the in vitro effects of VP 16-213 on L 1210 leukaemia cells and normal haemopoietic stem cells. They found that the dose-response curve was exponential and biphasic, although the normal haemopoietic stem cells were much less sensitive to the action of the drug. In fact, this method yielded the highest differential cytotoxicity between normal and leukaemic cells yet reported.

Cattan et al. [8] studied the effect of VP 16-213 on transplanted Lewis lung carcinoma in BDF_1 mice and found that although the drug had little effect on the volume of the primary tumour, it markedly reduced the number and volume of pulmonary metastases.

Mechanism of Action

Unlike podophyllotoxin, VP 16-213 does not produce metaphase arrest, but acts at an earlier stage in the cell cycle. Grieder et al. [31, 32], using a transplantable murine mastocytoma cell line, suggested that the drug arrests cells in late S or G_2 phases of the cell cycle. These results have since been confirmed by others [47]. Drewinko and Barlogie [21] looked at the effect of VP 16-213 on human lymphoma cells; synchronized cells showed age-dependent sensitivity, with the greatest lethal damage experienced by cells in the S and G_2 phases. Delay of cells in G_2 was dependent on an exposure time and concentration gradient; however, at very high concentrations a 'frozen state' of the whole cell cycle was observed.

Grieder et al. [31] studied macromolecular synthesis in VP 16-213-treated murine mastocytoma cells. While the mitotic index and proliferation of cells decreased, the cellular content of DNA, RNA, and protein continued to increase; this finding would be expected if the drug does not block the passage of cells through the S phase. Nucleoside incorporation studies performed at the same time showed little correlation, uridine and leucine uptake being enhanced at low drug concentrations, while high concentrations reduced incorporation. Thymidine uptake was reduced by 60%–80% by either concentration of drug. Loike and Horwitz further investigated nucleoside uptake in podophyllotoxin- and VP 16-213-treated HeLa monolayers and demonstrated that both drugs reversibly inhibited the uptake of uridine, thymidine, adenosine, and guanosine, all of which have distinct transport pathways. Studies by Wang and Chervinsky [64] demonstrated that labelled thymidine incorporation into DNA is time-dependent, with significant inhibition occurring by 2 h.

Loike and Horwitz [43] also studied the effect of VP 16-213 on HeLa cellular DNA, using alkaline sucrose gradient sedimentation profiles of radioactive DNA. High-molecular-weight DNA was converted to low-molecular-weight DNA, and the authors interpreted these changes as indicating DNA breaks induced by VP 16-213. Because the breaks were reversible on removal of the drug from the culture system it was suggested that these were single-stranded breaks, since double-stranded breaks are not normally repaired. Isolated purified HeLa and adenovirus DNA is not broken by the drug, indicating that the effect is not a result of direct chemical cleavage. VP 16-213 may activate one of several cellular endonucleases, or alternatively the drug may be metabolised to a directly acting metabolite.

Studies of congeners of podophyllotoxin and VP 16-213 have been carried out in attempts to establish which parts of the molecule are responsible for the respective differing biological activities. While podophyllotoxin completely inhibits microtubular assembly in vitro [11], VP 16-213 *has no effect* even at high concentrations. 4′-Demethyl-epipodophyllotoxin, the nonglucoside congener of VP 16-213, also inhibits microtubule assembly, which leads to the conclusion that it is the presence of the glucoside moiety that is responsible for this difference in action. Thus the inhibitory activity of podophyllotoxin derivatives on microtubule assembly is sensitive to the configuration and size of substituents at position 4 in ring C. The glucoside moiety itself is not neccessary for the entirely different biological effect of VP 16-213, which is now thought to be due to the presence of a 4′ hydroxy group at position 4′ of ring E. [44] (Fig. 1). Interestingly, there are several nonglucoside podophyllotoxin derivatives, e.g., 4′-demethylpodophyllotoxin, 4′-demethyl-deoxypodophyllotoxin, and 4′-demethylepipodophyllotoxin, all of which have a 4′ hydroxy group at position 4′ of ring E, which combine both the inhibitory actions on microtubule assembly and the ability to induce breaks in DNA. Obviously, these agents deserve careful consideration as potential antitumour agents.

Pharmacology

The drug is available in an IV form (100 mg in 5 ml ampoules) and two oral forms, a gelatin capsule and 5-ml drinking ampoule (both 100 mg). The capsules are large and some patients experience difficulty in swallowing them but they may be more acceptable than the drinking ampoule, as the drug has an unpleasant taste that can be only partially disguised by dissolving in fruit juice.

Using a tritium label, Creavan and Allen [2, 15] investigated the clinical pharmacology of the drug in a small group of patients following a 30-min IV infusion. The plasma decay fitted a bi-exponential equation and a simple two-compartment open model. The renal clearance is low (calculated mean clearance = 13.56 ml/min) and the elimination phase of plasma decay is moderately long (mean half-life 11.5 h). The mean volume of distribution is 28.9% of the body weight. In vitro analysis of protein binding to human serum albumin has suggested that at typical plasma concentrations the drug is 94% bound. Total recovery of labelled drug was 43.5%, of which 66.8% was unchanged drug. Faecal recovery was very variable (range 1.5%–16%) and an unexpected finding was the low concentration of drug in the CSF, particularly in view of its high lipid solubility.

When the drinking ampoule is used, absorption from the gastrointestinal tract is about 50% of the administered dose [7]. An early form of the gelatin capsule showed very variable absorption and excessive gastrointestinal toxicity [5, 28, 50, 52]. However, it has now been reformulated, and Beveridge et al. [6] showed that

there was no significant difference in absorption or disposition between this new capsule and the equivalent dose administered as the drinking ampoule.

Allen and Shirley [3] studied the uptake of VP 16-213 into mouse leukaemia L 1210 cells and found that the drug was taken up by passive diffusion. At steady state the intracellular concentration of the drug was twenty times the extracellular content. Efflux was mono-exponential, with a half-life of 2.7 min, until a final plateau phase was reached. Twenty percent of the drug was irreversibly retained in the cells, and the residual plateau level could be increased by vinblastine.

The fate of unexcreted VP 16-213 is unknown, but recently a urinary metabolite, 4'demethyl-epipodophyllic acid, has been described. Preliminary studies in L 1210 leukaemia suggest that the drug and metabolite have contrasting effects on either nucleoside transport or utilisation [4].

Phase-1 Studies and Dose Schedules

The recommended doses and schedules from the six reported phase-1 studies are shown in Table 1. No one schedule or route of administration has emerged as superior. Most of the early schedules were derived empirically and were based either on in vitro and animal studies or on the recommendations of the NCI for the investigation of new drugs. Since the studies of Falkson et al. [64] and Nissen et al. [50], the formulation of the gelatin capsules has been changed from a suspension to a solution, and the absorption and bioavailability is now similar to that of the drinking ampoule [5].

Table 1. Phase 1 studies with VP 16-213

Reference	Schedules
Nissen et al. [49]	45 mg/m² IV daily for 7 days; 69–86 mg/m² IV twice weekly for 3 weeks
Creavan et al. [16]	290 mg/m² IV weekly (1-h infusion), with modifications for toxicity
Eagan et al. [22]	125 mg/m² IV daily; 3 doses every 4 weeks
Falkson et al. [28]	300–400 mg/m² in capsule form over 5 days; marked gastrointestinal toxicity noted
Nissen et al. [50]	Up to 300 mg/m² in capsule form over 5 days; marked gastrointestinal toxicity noted
Nissen et al. [51]	120 mg/m² oral drinking ampoules for 5 days, with escalation according to toxicity

In an attempt to compare the biological activity of VP 16-213 given IV and PO both as capsules or drinking ampoules, Brunner et al. [7] randomised patients to receive either 300 mg/m² IV or 600 mg/m² orally as capsules or drinking ampoules over 3 days. Activity was reflected primarily by changes in the leucocyte or platelet count. The study incorporated a cross-over design whereby patients on capsules were changed to drinking ampoules after two courses, and vice versa. Although the numbers in each group were small, they concluded that the drug was more effective when administered as the drinking ampoule than when either the capsule or IV administration was used; however, it is not stated which type of gelatin capsules were used. As the drinking ampoule dose was half that of the IV dose, this suggests over 50% absorption. An alternative explanation is that prolonged plasma levels due to the administration three-times daily, may be responsible for the enhanced biological effect.

Sustained plasma levels of VP 16-213 have been explored by Smith et al. [57], who, in an unrandomised study, administered VP 16-213 as a prolonged (24-h) infusion to four patients. This mode of administration has theoretical attractions on kinetic principles, as the drug is highly phase-specific. This is further supported by the animal studies of Dombernowsky and Nissen mentioned above [18]. Clearly, further studies of this mode of administration in man will be needed before it can be recommended.

Phase-II Studies

Classic phase-II studies were performed by the EORTC [26] and Jungi and Senn [35]. Many tumour-orientated studies have since been performed, and the data are summarised in Tables 2–4. Only those studies clearly giving currently accepted criteria for complete or partial response have been included. Tables 2 and 3 list tumours according to a response rate of over (Table 2) or under 20% (Table 3). As with all such data, these response rates are achieved mainly in patients who have had extensive prior chemotherapy, and furthermore, the dose, schedule, and route of administration differ widely

Table 2. Tumours with a response rate greater than 20%

	Number evaluated	Response
Acute myelomonocytic leukaemia	18	39%
Small-cell anaplastic, lung	197	43.1%
Squamous-cell, lung	25	20%

[57, 26, 35, 10, 23, 61, 46, 13, 33]

Table 3. Tumours with response rate less than 20%

	Number evaluated	Response
Adenocarcinoma, lung	30	13.3%
Acute myeloid leukaemia	32	18.7%
Breast	60	5%
Colorectal	59	0%
Head and neck	31	3.2%
Hodgkin's disease	48	14.5%
Melanoma	61	1.6%
Non-Hodgkin lymphoma	87	13.7%
Ovary	39	10.2%
Soft-tissue sarcoma	17	0%

[64, 57, 26, 35, 46, 11, 9, 20, 25]

Table 4. Tumours for which less than 14 patients have been evaluated

	Number evaluated	Number responding
Acute lymphatic leukaemia	12	0
Acute monocytoid leukaemia	10	5
Bladder	9	1
Cerebral	2	0
Cervix	5	0
Endometrium	8	0
Kidney	4	1
Large-cell anaplastic, lung	5	0
Mesothelioma	5	0
Oesophagus	6	1
Osteosarcoma	5	0
Prostate	2	0
Stomach	9	0
Testis	4	0
Thyroid	1	1
Vagina and vulva	2	0

[28, 26, 35, 46]

from one study to another. Clearly, the efficacy of the drug is more likely to be reproducible when a large number of patients with a particular tumour type have been studied, e.g., small-cell anaplastic bronchial carcinoma (197 patients studied: response = 43.1%) or breast tumours (60 patients studied: response = 5%). Table 4 lists tumours where less than 14 consecutive patients have been studied, and in this situation, as Gehan [30] has pointed out, the chance of missing a response rate of 20% is greater than 1 : 20.

Small-Cell Bronchial Carcinoma

VP 16-213 is the most active single agent yet known for this responsive tumour, and for comparison the response rates for other active agents are shown in Table 5. Table 6 outlines some recent studies that have

Table 5. Active drugs in small-cell bronchial carcinoma

	Number evaluated	Response
VP 16-213	197	43.1%
Vincristine	43	42%
Adriamycin	36	31%
Methotrexate	73	30%
Hexamethylmelamine	69	30%
Cyclophosphamide	189	28%
CCNU	76	11%

Adapted from R. B. Livingston [41]

utilised VP 16-213 as a single agent. Differing schedules and routes of administration have been used, but even so, a consistently high response rate is seen, particularly as many patients have had extensive prior treatment. Cavalli et al. [10] (Table 6) randomised patients to three different schedules and concluded that the best results were obtained when 500 mg/m^2 was given as drinking ampoules, the dose divided over 3 days and repeated weekly. In general, cross-resistance with other commonly used agents in this disease has not been found, although Eagan et al. [23] suggested that initial treatment with high doses of an alkylating agent may prejudice subsequent response to VP 16-213.

When VP 16-213 is used as a single agent the response, although occurring in a large number of patients, is usually short-lived (approx. 100 days), and complete responses are few. Recently, however, Tucker et al. [61] reported on 47 patients (Table 5) who received VP 16-213 at a dose of 60 mg/m^2 IV daily for 5 days and subsequently twice weekly at the same dose in drinking ampoules. Further courses were given every 14 days if the blood count was normal, and treatment was continued until disease progression. Twenty-six patients were previously untreated, nine had received prior radiotherapy, and twelve had received prior chemotherapy. There were nine complete responses and fifteen partial responses, giving an overall response rate of 51%, and all but two patients showed an improvement in performance status. The overall median survival was 225 days (278 limited disease; 180 extensive disease). Three patients were alive and working 28 months after starting treatment, two of whom had received VP 16-213 as the only mode of treatment. Thus when used intensively as a single agent, as in this study, VP 16-213 produces results approaching those achieved with combination chemotherapy, but, with much less toxicity.

Non-Small-Cell Bronchial Carcinoma

The response rates for the three main non-small-cell tumours are shown in Tables 2 and 3. Eagan et al. [24]

Table 6. VP 16-213 in small-cell bronchial carcinoma

Reference			No. eval.	CR	PR	Percentage response
Eagan et al. [23]		125 mg/m² IV on days 1, 3, and 5, repeated every 4–5 weeks	16	–	7	37.5%
Cohen et al. [13]		200–300 mg/m² IV weekly; dose reduction based on blood count	16	–	4	25%
Hansen et al. [33]		100 mg ampoules twice daily for 4–5 days; repeated every 3 weeks	40	–	20	50%
Tucker et al. [61]		60 mg/m² IV daily for 5 days + 60 mg/m² orally twice weekly between IV courses; repeated every 14 days	47	9	15	51%
Cavalli et al. [10]	Randomised	250 mg/m² IV once weekly	20	1	3	20%
		500 mg/m² ampoules divided over 3 days; repeated weekly	17	2	9	65%
		850 mg/m² ampoules divided over 5 days; repeated every 3 weeks	19	2	6	42%
			175	14	64	44.5%

treated 44 previously untreated patients (20 squamous, 24 adenocarcinoma) with 140 mg/m² IV on days 1, 3, and 5, repeated every 4–5 weeks until disease progression. Five patients with squamous-cell carcinoma and three (12.5%) with adenocarcinoma had partial regressions. These figures, although derived from small numbers of patients, suggest that VP 16-213 is in the same activity range as most other single agents to which these tumours respond. The number of patients with large-cell anaplastic carcinoma reported in phase-II studies is too small to be meaningful.

Acute Leukaemias

In the phase-II study conducted by the EORTC [26], four of eight patients with monocytic leukaemia (2 monocytoid; 2 myelomonocytic) were reported to have had a complete remission, and in the study reported by Mathé et al. [46], five of sixteen patients (3 monocytic, 2 myelomonocytic) achieved complete remission. The two patients with myelomonocytic tumours who achieved remission had previously been resistant to cytosine arabinoside. Even in patients failing to achieve complete remission, the disappearance of monocytic cells was noted. In total, 9 of 28 patients (32%) with a monocytic type of leukaemia have had complete remissions. No explanation has been advanced for the high responsiveness of this variant of acute leukaemia. On the other hand, only 3 of 32 patients (9.3%) with classic acute myeloid leukaemia have achieved complete remission when treated with VP 16-213 alone. No remissions, complete or partial, have been observed in a toal of 12 patients with acute lymphatic leukaemia.

Lymphomas

No complete remissions have occurred in 48 patients with Hodgkin's disease or 87 patients with non-Hodgkin's lymphomas. The respective partial response rates are 14.5% and 13.7%, and adequate numbers have probably been evaluated for both diseases. Thus the drug can only be recommended when first-line agents have been tried and failed. The drug may, however, be useful for incorporation into experimental combinations in attempts to develop new non-cross-resistant regimes for patients who have relapsed on conventional therapy.

Breast, Head and Neck, Melanoma, Ovarian, and Soft-Tissue Sarcoma

In these tumours the drug has been evaluated in sufficiently large numbers of patients to ascertain that they are relatively unresponsive, and further studies are not warranted at present.

Other Tumours

For the tumours listed in Table 3, insufficient numbers of patients have been studied to allow firm conclusions

about response rate. For some, e.g., bladder, thyroid, and prostate, especially where hints of activity have been shown, it may be justifiable to perform further tumour-orientated phase-II studies. For other tumours, e.g., acute lymphatic leukaemia, where there are many active agents, no further studies are justified. In addition to figures published, unpublished data suggest that the drug may also have a place in the management of patients with advanced malignant teratomas, choriocarcinoma (T. McElwain and E. Newlands, personal communication, 1978) and hepatocellular carcinoma (W. Melia and R. Williams, personal communication, 1978).

Combination Chemotherapy

VP 16-213 is suitable for combination with many other agents, as it appears to have relatively little toxicity and a mode of action unique to itself and its close congener VM 26. Empirically derived combinations are already entering full phase-III studies for the management of small-cell bronchial carcinoma (Table 7).

Dombernowsky and Nissen [19] used the L 1210 leukaemia system to examine combinations of VP 16-213 with other agents. Combinations with cyclophosphamide and CCNU were the only ones to demonstrate a 'more than additive effect', and the combination of VP 16-213 with vincristine actually proved to be inferior to VP 16-213 alone. This may be of practical interest, as vincristine is another drug commonly used to treat small-cell carcinoma. In a further study, Rivera et al. [54], also using the L 1210 system, demonstrated that VP 16-213 can potentiate the effect of treatment with cytosine arabinoside.

Extrapolation of experimental data to the clinical situation is notoriously precarious; however, carefully designed trials should be devised to test these combinations in man. VP 16-213 and cytosine arabinoside is a potentially attractive combination for the management of acute monocytic leukaemia or acute myelogenous leukaemia with a large monocytic component, while VP 16-213 in combination with cyclophosphamide or CCNU should be tested in patients with small-cell bronchial carcinoma.

Toxicity

The two dose-limiting toxic effects are myelosuppression and gastrointestinal disturbances. Neutropenia occurs around day 8–10, with thrombocytopenia usually occurring 2–3 days later [35]. Bone marrow recovery is rapid and usually complete by the day 20. Septicaemia has been reported infrequently, and usually only occurs in patients on high-doseage schedules. No cumulative toxicity has been noted in any of the trials reported to date.

Gastrointestinal disturbances occur in about 25% of patients, but are usually easily controlled. The early form of gelatin capsule, which has now been reformulated [6] produced excessive toxicity and erratic absorption; however, the new capsules are well tolerated and appear to be more acceptable than the unpleasant-tasting drinking ampoules. Both oral preparations are more likely to produce gastrointestinal disturbances than is the parenteral form [7].

Alopecia occurs in about 33% of patients, but is usually less severe than that produced by adriamycin or cyclophosphamide. There have been no documented abnormalities of renal function, and hepatotoxicity has not been proven conclusively, although Cecil et al. noted transient jaundice and elevation of alkaline phosphatase in two patients. A liver biopsy in one of these patients showed changes compatible with either viral hepatitis or drug toxicity [11].

Hypersensitivity reactions with fever, and occasionally hypotension, have been noted [68], and it is recommended that when the drug is administered for the first

Table 7. Current randomised trials utilising VP 16-213 for the management of small-cell bronchial carcinoma

NCOG, USA		VP 16 + ADRIA + MXT PROCARB + VCR + CYCLO + CCNU
University of Southampton, England		VP 16 + ADRIA + LOW-DOSE MXT VP 16 + ADRIA + HIGH-DOSE MXT + LR
University of Miami, USA		VP 16 + ADRIA + PROCARB CYCLO + MTX + VCR
WPL Group, Rosswell Park, Buffalo, USA		VP 16 + ADRIA + VCR VP 16 + ADRIA + VCR + LEVAMISOLE
Swiss Group, Berne, Switzerland		VP 16 + MTX + VCR + CYCLO PROCARB + VCR + MXT + CYCLO
ECOG, USA	Failed on prior therapy	VP 16 + ADRIA VCR + ADRIA

time a small test dose is given before the first IV injection. Substernal discomfort and palpitations were noted in a few patients taking the early capsule preparation, but this has not been noted since. A myocardial infarction occurred in a 27-year-old woman, and raised the question of drug-induced coronary-type cardiotoxicity [56].

In summary, the toxicity of this compound is markedly lower than many other agents currently in use. It is usually predictable and reproducible, and discontinuation of therapy is virtually never necessary.

Conclusion

VP 16-213 is a new semisynthetic podophyllotoxin derivative, which appears to have a unique mode of action and the advantage of both oral and IV administration. Early promise of activity in small-cell bronchial carcinoma has been sustained, and the single-agent response rate remains at over 40% with nearly 200 patients studied. It also shows promise as an active agent in patients with acute monocytic or myelomonocytic leukaemia and possibly malignant teratoma. In the next few years its role will be more fully defined by the results of the current phase-III studies. The podophyllotoxin ring system is an ideal structure for further modification in attempts to discover other antitumour agents.

Acknowledgements: I would like to thank Mrs. Englefield for secretarial help in the preparation of the manuscript. This work was completed during tenure of a Gordon Hamilton Fairley Research Fellowship.

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Received December 12, 1978/Accepted February 22, 1979