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Abstract

Naturally Occurring Mammalian Lignans

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Lignans are a class of compound having a 2,3-dibenzylbutane skeleton. They are uncommon plant constituents but have received attention because many plant lignans and synthetic analogues have been shown to exhibit antimitotic activity and have therefore been investigated as potential anticancer agents. Recently a number of naturally occurring mammalian lignans were identified for the first time in the urine bile and feces of humans, monkeys and rats. Two of the principal compounds, identified by GC-MS and NMR spectrometry as *trans*-2,3-bis(3-hydroxybenzyl) butyrolactone and 2,3-bis(3-hydroxybenzyl)butane-1,4-diol were of novel structure. Their racemic nature excluded a direct dietary origin since all known plant lignans exist in optically pure forms. Studies of the physiological characteristics of these new compounds showed that they were present in human urine in relatively high levels (0.2–2 mg/day) almost exclusively as the glucuronide conjugate and that they exhibited a cyclic pattern in excretion in women. Studies in rats established that they undergo an enterohepatic circulation and are produced by intestinal microflora. Selective antibiotic administration to humans has shown that anaerobic bacteria, possibly clostridia, are responsible for the production of these lignans although the biosynthetic pathway is presently unknown. Preliminary studies have indicated that the lactone has a cytotoxic effect upon human lymphoid cells. These observations raise intriguing questions of whether lignans play a role as anticancer agents or whether by the nature of their chemical structure they may be carcinogenic.

A Novel and Facile Route to Podophyllotoxins

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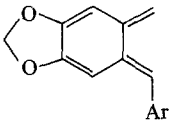
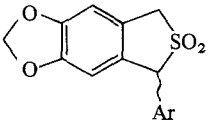
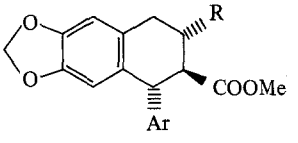
A short and flexible synthesis of the basic ring system of the podophyllotoxins has been developed. The key reaction is a thermal cycloaddition reaction between dienes like (I), formed from sulphones of type (II), and olefines to give good yields of cycloadducts like (III) and (IV). Both compounds can be chemically modified to yield (±)-podophyllotoxin and analogues, but present work is directed towards the synthesis of fluoro- and trifluoromethyl-cycloadducts like (V) in order to prepare modified podophyllins. The known propensity of fluorine to alter the profile of biological activity of compounds, as well as the inability of compounds like (VI) to epimerise, will, we hope, confer useful activity on these synthetic compounds.



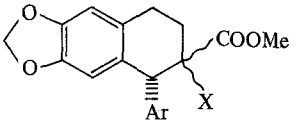
(I)



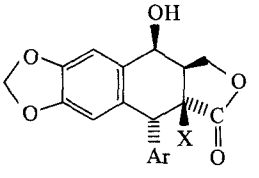
(II)



(III) R=H
(IV) R=CO2Me



(V) X=E or CF_3



(VI) X=F or CF_3

Is the Lactone Moiety of VP16-213 Necessary for Activity? Synthesis and Activity of VP16-213 Cyclic Ether

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It is not known whether the lactone of VP16-213 is an absolute requirement for activity of this drug. That is,

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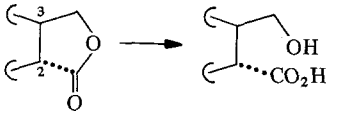
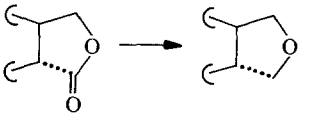
the lactone could be an essential alkylating moiety of VP16-213. Further, the lactone is readily metabolized in vivo to the inactive ring opened hydroxy-acid:



In an attempt to eliminate this metabolic detoxification pathway and to examine whether the lactone is an essential reactive or structural feature for activity of VP16-213, we have synthesized the corresponding cyclic ether of the drug:



The cyclic ether has been tested in the mouse leukemia L1210 system and appears to retain activity relative to VP16-213. This suggests that the lactone is not an absolute requirement for activity of VP16-213.

In the synthesis of VP16-213 cyclic ether, considerable use was made of high resolution (470 MHz) nuclear magnetic resonance (NMR) spectroscopy, particularly in the determination of the cis- or trans-fused configuration of the ether at positions C-2 and C-3.

Studies on the Metabolism of VP16-213 in the Rat

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The metabolism of VP16-213 in vitro by rat liver systems and in vivo by the rat has been studied. VP16-213, specifically labelled with tritium at position C-1 and with a specific activity of 119.8 μCi/mg, was incubated with rat liver microsomes and rat liver homogenates, and metabolism extracts analysed by high-performance liquid chromatography (HPLC) with UV- and radioactivity detection. For control incubations, VP16-213 was incubated only in buffer and in homogenates and microsomes inactivated by heating at 85–90° C for 20 min. After HPLC of metabolism extracts (ethanol/aqueous mixtures), eluate fractions were subjected to liquid scintillation counting, and percentage radioactivity distributions of chromatograms were calculated. It was found that VP16-213 was metabolised extensively by rat liver homogenates and by rat liver microsomes, with the formation of one major metabolite. After HPLC on a reversed-phase microparticle C_{18}-column using isocratic elution with a mixture of methanol-water, 40 : 60 (v/v%), buffered at pH 7.1 with 0.01 M potassium phosphate, VP16-213 showed a retention time varying between 8.5–9 min for the incubations in various systems. Incubations with rat liver homogenates showed the presence of a major radioactive product with short retention time (3 min), not present in control incubations. In one experiment this metabolite was present at a level of 39.5% of total radioactivity after 4 h of incubation with rat liver homogenate. Two other minor components with retention times 5 and 7 min were found to be produced after incubation with liver homogenates, but their formation was not reproducible. The major metabolite formed by liver homogenates was also present in methanol −, but not in chloroform extracts of plasma samples of rats, treated with VP16-213. Two hours after two consecutive i.p. injections, corresponding to doses of 1.1 mg/kg, with an interval of 3 h, the metabolite was found to be present in the plasma at a level of 45% relative to VP16-213. The short retention time of the metabolite in reverse-phase chromatography, which coincides with that of the synthetic cis-hydroxy acid derivative of VP16-213, and solubility properties, suggest the metabolite to be the cis- or trans-hydroxy acid derivative of VP16-213. On account of the performed experiments, the metabolite is formed by an enzyme present in the microsomal fraction of rat liver.

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Pharmacokinetics and Bioavailability of VP16-213 in Man

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VP16-213/Pharmacokinetics/Bioavailability/ Analysis in Plasma and Urine

Levels of VP16-213 have been measured in the plasma and urine of patients receiving the drug as part of chemotherapy regimes by high-pressure liquid chromatography. The analytical method involves extraction into chloroform using VM26 as internal standard and chromatography on a Hypersil-ODS column (100 × 5 mm) with 52% methanol as the eluting solvent.

By using UV detection at 225 nm the lower limit of detection is less than 100 mg/ml in a 0.5 ml plasma sample. In patients receiving VP16-213 (200 mg/m^2) as an intravenous infusion over 30 min. The drug follows either 2 or 3 compartment kinetics, with half-lives of the second phase of 6–8 h, and of the third phase (where detected) of 20–46 h.

Bioavailability has been assessed in five patients who have received 400 mg VP16-213 both as an i.v. infusion and orally in capsules, and estimates of bioavailability using both area under the curve and urinary recovery methods range from 48%–78%.

Renal clearance of VP16-213 is about 10–15 ml/min, and accounts for one third of the total plasma clearance.

Sensitive High Performance Liquid Chromatographic Analysis of VM26, VP16-213 and Cis-Hydroxy Acid of VP16-213 Using UV and Electrochemical Detection

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This paper presents a rapid and sensitive high performance liquid chromatographic assay of the two antineoplastic podophyllotoxine analogs VP16-213 and VM 26 in plasma and urine. The drugs are extracted after adding of an internal standard (Ethyl ester of p-hydroxy benzoic acid) with 1 ml chloroform. After washing and evaporation of the organic layer the extracts are chromatographed on a Lichrosorb reversed phase C18 column using uv detection at 280 nm. Quantitation is based on peak height ratios. The quantitation limits are 30 ng VP16-213/ml plasma and 50 ng VM26/ml plasma. This paper also presents an hplc method for the analysis of the cis-hydroxy acid of VP16-213, an isomer of a possible metabolite of VP16-213. Since no synthesis of this metabolite, trans-hydroxy acid of VP16-213, has been reported the investigations are carried out on the cis-isomer. Lower quantitation and detection limits of VM26, VP16-213 and possible metabolites, due to higher sensitivity and selectivity, will be achieved by using an hplc method with electrochemical detection. The applied electrochemical detector consists of a flow-through cell with two glassy carbon (Work and auxilliary) electrodes and an Ag-AgCl reference electrode. The electrochemical potential is set at +1100 mV vs. Ag/AgCl reference electrode. The detection limit of VP16-213 in this system is 100 pg absolute amount injected. Further preliminary clinical pharmacokinetic results will be presented.

Analysis of VP16-213 and VM26 in Plasma by High Performance Liquid Chromatography with UV and or Fluorescence Detection

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A rapid, convenient, sensitive and specific high-performance liquid chromatographic (HPLC) procedure for the analysis of plasma levels of VP16-213 and VM26 has been developed.

The drugs are extracted from plasma with chloroform. The extracts are then evaporated to dryness, reconstituted in methanol, and chromatographed on a reverse-phase microparticle C_{18} column using isocratic elution with a mixture of methanol and water (60 : 40). Each drug is used as the internal standard for the other. Quantitation to 500 ng/ml (850 pmole/ml) of plasma is obtained using UV detection at 254 nm and measuring peak height ratios.

The drugs can be quantitated conveniently to at least 50 ng/ml (85 pmole/ml) of plasma when fluorescence detection of these compounds is employed (excitation at 215 nm; emission at 328 nm). The increased sensitivity of the fluorescence assay allows quantitation of these drugs in plasma to at least 48 h with normal dosages. The increased specificity of fluorescence detection also allows quantitation of VP16-213 and VM26 in the presence of coadministered drugs which can interfere with the UV assay.

A Phase I–II Trial of Continuous Infusion VP16-213

D. A. Van Echo, J. Aisner, M. Whitacre, P. H. Wiernik. Baltimore Cancer Research Program, DCT, NCI, Baltimore, Maryland 21201, USA

Since there appears to be a time-dose response relationship for VP16-213, the current dose seeking study of 5 day continuous infusion was initiated on a q 3 week schedule. Patients not candidates for other treatments were started at 75 mg/m^2/day × 5 day and subsequent trials were escalated if there were acceptable toxicity. All patients had received prior chemotherapy and 5/9 had received prior irradiation. The tumors included: metastatic basal cell CA (1), Breast CA (1), colon CA (2), squamous lung cancer (1), oat cell (2), periosteal sarcoma (1) mixed mesodermal tumor (1). The median age was 55 (range 31–65) and the median performance status was 70 (range 50–90).

The nine patients received a total of 14 courses: two at 75 mg/m^2/day, 4 at 100 mg/m^2/day and eight at 125 mg/m^2/day. Non-hematologic toxicity was mild with nausea and vomiting in three patients, mild mucositis in one, and diarrhea in two. Hematologic toxicity was acceptable at all levels. Median WBC count nadirs (ranges) were: 3.5 (2.3–4.7) × 10^3/μl, 1.6 (0.2–3.4) × 10^3/μl, and 1.5 (0.2–3.6) × 10^3/μl for the 75, 100, and 125 mg/m^2/day doses respectively. The median days to nadir (16) and days to recovery (21) were the same for all dose levels. Median platelet count nadirs (ranges) were: none, 133 (24–189) × 10^3/μl, and 110 (26–326) × 10^3/μl for the three respective dose levels with a median of 12 days to nadir. There have been no antitumor responses yet among the four patients evaluable for response. The current study demonstrates that high dose continuous infusion VP16-213 is tolerable with acceptable toxicity using doses up to 625 mg/m^2 over 5 days. Further ecalations are planned to examine toxicity and response.

Hepatic Arterial Infusion (HAI) of VP16-213 for the Treatment of Metastatic Disease Confined to the Liver

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Five patients with colorectal carcinoma (CRC) and two patients with adenocarcinoma of the lung confined to the liver were treated with HAI of VP16-213 in a phase I–II trial aimed at determining the feasibility and activity of VP16-213 given by HAI in CRC and lung cancer. Three of the five CRC patients were previously treated with a nitrosourea and 5-FU, and the lung cancer patients with cytoxan, adriamycin and Cis-platinum combination. The dose of VP16-213 was 80–100 mg/m/day × 3 days given via a percutaneously placed catheter. Response was determined by imaging techniques (ultrasound, CT scan and angiography) and by changes in serum level of carcinoembryonic antigen. None of the CRC patients showed any evidence of response while in both lung cancer patients some antitumor effect (< PR) was observed. In two of five colon cancer patients a dose of 100 mg/m^2 × 3 or 80 mg/m^2 × 3 was associated with significant myelosuppression resulting in fatal septicemia in one patient. In the other three CRC patients blood counts were not affected. To evaluate this variability in bone marrow sensitivity to HAI of VP16-213 we decided to compare the pharmacology of HAI and IV administration of VP16-213. Data will be presented regarding this comparison. We conclude that although HAI of VP16-213 is probably feasible it has a questionable role in the management of liver metastases from CRC. It might however play a role in palliation of metastatic adenocarcinoma of the lung confined to liver. Its role in the management of hepatocellular carcinoma will be studied at a later phase.

Podophyllin Increases Tumor Radioresponsiveness

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Two case reports suggest that topical podophyllin and visible light enhance the tumoricidal effect of ionizing radiation upon infiltrating ductal carcinoma (all receptors −) and the giant condyloma of Buschke-Loewenstein. The latter is a rare low grade invasive malignancy, against which podophyllin, ionizing radiation, and chemotherapy have been reported to be individually ineffective. A cobalt 60 irradiator was used to treat the 12 × 11 cm ulcerating right anterolateral chest wall mass (0.5 cm gelatin and packed wet gauze as bolus, thin wedge : open = 3 : 1). 50.0 Gray was delivered to the midbreast at axis (48 days, 25 fractions, TDF = 79). A linear accelerator (10 MeV X-rays) was used to treat the 15 × 10 cm rectal lesion. A four-field box technique was used with a 1.5 cm bolus. Total dose was 54.2 Gray (127 days/30 fractions. TDF = 83, dose rate 100 centigray per minute). Topical podophyllin (25% tincture of benzoin) was applied once per day to some of the available exterior surfaces (20 min before the treatment, 4 ml, 4 days a week, washed off 4–8 h later). Control volumes included painted normal tissue, and tumor solely x-irradiated. The visible light was 18.4 mW/cm^2 with 1 cm of water used to filter the infrared component. Friable oozing tumor ceased bleeding in days. Radiographic and morphometric semiquantitative analysis confirmed a more rapid tumor regression where the combined therapy was used. The rectal lesion became 13% of its initial area by the end of 5 days of combined treatment (600 centigray combined treatment, 2,000 cGy X-radiation only).

The corresponding volume receiving radiation only decreased to about 56% of its size. Over 2 months the podophyllin painted volumes softened, flattened, liquified, sloughed, and granulation tissue briskly proliferated. Biopsy of the ductal carcinoma revealed a histologic paucity of viable tumor cells, only in the volume treated with all modalities. There

was hematopoetic depression. The rectal patient complained of pain as the tumor sloughed, which was treated symptomatically by oral analgesics. Allopurinol was used prophyllactically to protect against hyperuricemia.

Antiinvasive Effect of Podophyllotoxins in vitro

M. Mareel, C. Dragonetti, R. Van Cauwenberge, G. De Bruyne. Laboratory of Experimental Cancerology, Clinic of Radiotherapy and Nuclear Medicine, Academic Hospital, Ghent, Belgium

Invasiveness contributes to the malignancy of solid tumors. Using an in vitro assay of invasiveness we have provided evidence that some chemotherapeutic agents inhibit proliferation but allow invasion, whereas others inhibit both proliferation and invasion [Mareel and De Brabander (1978) J Natl Cancer Inst 61:787–792]. We report here the effect of podophyllotoxin and its derivatives VP16-213 and VM26 (Laboratories Bristol, Benelux N.V.) on the invasion of M04 mouse fibrosarcoma cells into embryonic chick cardiac muscle in organ culture. Podophyllotoxin (0.1 μg/ml), VP16-213 (10 μg/ml), and VM26 (1 μg/ml) inhibit the growth of M04 spheroids. At these concentrations podophyllotoxin is antiinvasive, but VM16-213 and VP26 permit invasion. We have reported that inhibition of invasion in organ culture can be predicted from inhibition of directional migration of M04 cells from a spheroid explanted in tissue culture [Storme and Mareel (1980) Cancer Res 40:943–948]. This is also the case with VM26 and VP16-213. Immunocytochemical staining with tubulin antiserum (kindly provided by M. De Brabander and J. De Mey) shows that podophyllotoxin abolishes the cytoplasmic microtubule complex in contrast with VP16-213 and VM26. Treatment with VP16-213 or VM26 produces large mononucleated cells, that are able to perform directional migration and to invade. Podophyllotoxin is a typical microtubule inhibitor, which produces C-mitoses and multimicronucleated cells. Like other microtubule inhibitors, podophyllotoxin not only inhibits proliferation but also interferes with the capacity of M04 cells to invade into normal tissues.

Phase 3 Studies with Etoposide (VP16-213) in Lung Cancer Patients

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Three multicenter prospective randomized studies are ongoing in lung cancer patients. Two studies are in small cell disease. One 2-arm study examines the substitution of etoposide (E) for vincristine (V) in cyclophosphamide (C), Adriamycin (A), and vincristine therapy; i.e., C.A.V. versus C.A.E. The other 3-arm study examines the addition of A to C.V. and the substitution of E for A in C.A.V.; i.e., C.V. versus C.A.V. versus C.E.V. All combinations are given to maximally tolerated doses. Eighty-one and 93 patients, respectively, have been entered into these two studies to date. The 2-arm study in non-small cell disease examines the substitution of E for A in cyclophosphamide, Adriamycin, and cisplatin (P) combination therapy; i.e., C.A.P. versus C.E.P. Sixty-seven patients have so far been entered into this study. Early interim analyses of these studies suggest a trend favoring the E-containing arms.

Monoagent VP16-213 in Bronchogenic Carcinoma and Report of Toxicity in Combination with Other Cytotoxics

G. Anderson, E. T. Peel. Newport Chest Clinic, 129 Stow Hill, Newport, Gwent, Great Britain

Eighty patients with disseminated bronchogenic carcinoma received cycles of oral VP16-213 daily for 5 days. Fifty-four survived to receive two or more cycles and 23 showed an objective response. Remissions were commonest in small cell tumours but all cell types responded to some degree. Responders received a mean of seven cycles. The drug was well tolerated and only one patient developed leucopenia. This demonstration of monoagent effectiveness and safety led to four subsequent pilot trials of VP16-213 combined with other cytotoxics. Dangerous pancytopenia occurred when VP16-213 was combined with vincristine and two dose levels of methotrexate, with vincristine and adriamycin and with cyclophosphamide. The possible mechanism of this important drug reaction will be discussed.

VP16-213 Phase II Study Small Cell Lung Carcinoma

J. L. González Larriba, J. M. Montero Carcía, A. Ordoñez Gallego, and S. Juarez Alonso. Ciudad Sanitaria La Paz, Madrid, Spain

Forty-five patients with different types of neoplasias were treated with VP16-213 combined with other cytostatics. Twenty-one lung cancer (15 of them microcell), 14 breast cancer, five acute leukaemia, three lymphoma, one glioblastoma, one metastatic

cancer of an unknown origin. The best responses were obtained in lung microcell neoplasias: 11 responses (CR + PR) in 15 patients, seven of which had received prior therapy with unsuccessful results. Of the remaining 30 patients only eight responses were achieved (1 CR). Toxicity was primarily gastrointestinal but it was not necessary to suppress the treatment by this reason. No therapy related death occurred.

Oral Epipodophyllotoxin and Chlorambucil: A Preliminary Study in Small Cell Carcinoma of Lung

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Five patients with previously untreated small cell carcinoma of lung, who were considered unsuitable for aggressive intravenous chemotherapy, were treated with oral epipodophyllotoxin (100 mg tds alt die × 3) and chlorambucil (10 mg OD × 7) every 3 weeks. One had limited disease and four had extensive disease. This therapy was generally well tolerated, with the exception of one patient who experienced severe vomiting and was unable to continue the treatment. The four remaining patients all responded, with two CR and two PR. This oral combination of epipodophyllotoxin and chlorambucil would appear to achieve a good response rate, and has a place in the treatment of patients with small cell carcinoma of the lung who require chemotherapy, but are unsuitable for aggressive intravenous protocols.

VP16-213 in the Therapy of Small Cell Lung Cancer (SCLC). Preliminary Results in Combination Chemotherapy

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The role of VP16-213 in combination therapy for SCLC is undefined. Since Jan. 1977 we have treated 245 patients, with Lung cancer, 61 (24.6%) were small celled. Initially 41 were treated with CTX-ADR-MTX-CCNU at standard doses and the last 20 patients are being treated every 3 weeks with: A-(DDP 80 mg/m^2 i.v. CTX 600 mg/m^2 i.v. × 1 day VP-16 100 mg/m^2 p.o. × 5 day) or B. CTX 600 mg/m^2 i.v. VP-16 100 mg/m^2 p.o. × 5 day. CCNU 60 mg/m^2 p.o. × 1 day. No RT is administered with either treatment. Patient characteristics are: 17 M, 3 F. Mean age 62 range (45–75). Mean initial Karnofsky 60 (20–100). Initial stage of disease: III (82%) – II (2 patients) – I (1 patient). Four received treatment A and sixteen B. Only 16 patients could be evaluated and the total response rate T.R. was nine patients (56%): Two CR and seven PR by standard criteria. Haematologic toxicity was very mild: Hb declined more than 3 g in 60% but blood transfusions were not necessary. The total number of leucocytes never numbered less than 2,300 mm^3 thus a full dose administration was given in 70%. The platelet number was not affected. General side effects were mild and pt. acceptance was better with regimen B than A.

Combination Chemotherapy with Cisplatin, Etoposide and Adriamycin in Small Cell Bronchogenic Carcinoma

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Combination chemotherapy with cisplatin 60 mg/m^2 D1, etoposide 120 mg/m^2 D1-2-3 and adriamycin 45 mg/m^2 D1 has been used in 36 evaluable patients with small cell bronchogenic carcinoma. We observed a complete response rate of 23% in patients with disseminated disease and 59% in those with locoregional disease. The overall response rate was similar in the 2-groups (86% for locoregional and 82% for disseminated disease). The response was usually rapidly obtained (generally within 3 months).

The survival cannot still be completely evaluated: median survival time is superior to 14 months in limited disease and to 10 months in disseminated disease.

Side effects other than bone marrow toxicity were acceptable and consisted mostly of nausea, vomiting and alopecia. Hematologic toxicity was usually severe and three toxic deaths were noted.

VAM/POCC VS. POCC Chemotherapy of Small Cell Lung Carcinoma: Superiority of Early Alternation of Two Non-Cross-Resistant Combinations

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From October 1977 to May 1980, 153 patients with extensive stage small cell lung carcinoma were treated

according to NCOG Protocol No. 2061. Patients were randomized to initially receive either VAM (VP16-213, adriamycin, methotrexate) for three cycles or POCC (procarbazine, vincristine, cyclophosphamide, CCNU) for two cycles. All patients received 3,000 rads cranial irradiation during the 3rd cycle of VAM (weeks 8, 9) or 2nd cycle of POCC (weeks 7, 8), without interruption of chemotherapy. Those patients who received induction with VAM were then treated with alternating POCC and VAM, while the others continued with POCC. The VAM/POCC arm is superior to POCC with respect to complete remission rate (40% vs. 20%), median duration of response (6 vs. 4 months) and median survival (10 vs. 7 months). The initial rate of complete response was identical for VAM and POCC, 20% during the first 2 months of induction. An additional 20% of patients achieved complete remission when alternating POCC was introduced after initial VAM treatment. Therefore, VAM is clinically non-cross-resistant with POCC, when alternated early in the course of treatment. However, when treatment with VAM was delayed until after patients had failed treatment with POCC, only one of 15 patients had even a partial response. It thus appears that broad cross-resistance develops later in the course of treatment. Among patients treated with VAM/POCC, 10% are alive without evidence of disease 2 years after diagnosis, compared to none treated with POCC alone. Hematologic toxicity was equivalent, and neurologic toxicity less severe, for VAM/POCC compared to POCC.

A Phase II Study of VM26 in Previously Treated Patients with Small Cell Bronchogenic Carcinoma (SCC)

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Twenty-nine patients with histologically verified SCC were included in a phase II trial of VM26. The dose schedule was 60 mg/m^2 i.v. day 1–5 every 3 weeks. All patients were resistent to conventional combination chemotherapy. All but six had received VP16-213 in the previous treatment.

Previous VP16-213	Accrued	Evaluable	Response	
			PR	NR
+	23	17	1	16
−	6	3	0	3
Total	29	20	1	19

Performance status (ECOG) was for three patients: 0, nine patients: 1, nine patients: 2, eight patients: 3, no patients: 4. The duration of the PR was 6 + weeks. The hematological toxicity consisted of wbc < 2,000/mm^3 in 11 patients, thrombocytes < 100,000/mm^3 in 10 patients. Three patients developed septicaemia. Gastrointestinal toxicity was minor and caused in no patients cessation of therapy. No instances of hypotension was noticed. It is concluded that VM26 has minimal activity in patients previously treated with combination regimens containing VP16-213. With regard to patients not earlier exposed to Epipodophyllotoxins the number of patients is too small for any conclusions to be drawn.

VP16-213 in Consolidation Therapy of Small Cell Lung Cancer

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We have previously reported the activity of VP16-213 alone and in combination regimens in refractory germinal malignancies (Cancer 46: 2154, 1980), in refractory small cell lung cancer (AACR p 28, 1979) and in the initial consolidation therapy of small cell lung cancer (Cancer Chemother Pharmacol 4: 173, 1980). Over 250 limited stage patients have been entered in a study of combination chemotherapy with cyclophosphamide, adriamycin, and vincristine (CAV) ± regional radiotherapy (RT) to the primary chest lesion. Sixty-five patients have completed induction therapy (six cycles CAV ± RT) and 52 are evaluable after completing consolidation therapy with VP16-213 (200 mg/m^2 twice monthly) and Hexamethyludamine (HMM) (280 mg/m^2 daily X 14 each month) for three cycles. For the 27 on CAV, 67% have had a complete (CR) plus partial response (PR). Of the 38 on CAV plus chest RT, 84% achieved a CR + PR. Restaging was intensive including bronchoscopy in most patients. All patients received prophylactic cranial RT. Of the 52 patients evaluable for consolidation, 39 were in CR prior to consolidation and 85% of these patients remained in CR. Of the 13 who were in PR before VP16-213 + HMM, three (28%) achieved CR and two continued in PR. Therefore, 38% improved during consolidation therapy. A majority of patients had mild to moderate toxicity but over one-third had severe or life threatening toxicity (primarily granulocytopenia) with these regimens. Three toxicity related deaths have occurred. Toxicity with consolidation was mild

to moderate in most patients but onethird had severe gastrointestinal toxicity during VP16-213 + HMM therapy. While it is still early, preliminary evaluation of the induction phase of this protocol indicates a significantly higher CR rate may be achieved with combined modality therapy of this disease. The combination of VP16-213 and HMM is effective in inducing further responses in patients who have not achieved a CR on CAV or CAV + RT.

Chemotherapy with Etoposide and Cisplatin in non Small Cell Bronchogenic Carcinoma

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Since 1978, the EORTC Lung Cancer Working Party has initiated two clinical trials non small cell bronchogenic carcinoma with etoposide-containing regimes. In the first study, 87 evaluable patients have been treated with cisplatin 60 mg/m^2 day 1 and etoposide 120 mg/m^2 days 3-5-7. This therapy was repeated every 3–4 weeks. After two courses, the response rate was 45% in squamous cell carcinoma (CR 3/65, PR 26/65) and 32% in adenocarcinoma (CR 1/22, PR 6/22). Patients with locoregional disease and no prior therapy had a significantly higher response rate and median survival (51%–62 weeks) than patients with disseminated disease or pretreated locoregional disease. The second regimen used was identical plus vindesine (1.5 mg/m^2 days 1 and 8). Only partial data are available so far: the response rate is 9/17 in squamous cell carcinoma and 3/6 in adenocarcinoma, thus an overall response rate of 12/19 (63%).

Bleomycin VP16-213 and Cis-Platinum (BEP): A Lower Toxicity Combination for Selected Patients with Germ Cell Tumours

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A regimen in which vinblastine is replaced by VP16-213 has been employed in an attempt to reduce the toxicity of cis-platinum vinblastine and bleomycin (PVB) in patients referred with uncontrolled testicular non seminoma after unsuccessful radiation therapy. The severe gut toxicity encountered in recently irradiated patients, attributed to vinblastine, was reduced by employing the modified regimen. Encouraged by this experience the three drug combination of Bleomycin, VP16-213, and cis-platinum (BEP) has been introduced as first line treatment for patients with advanced non-seminoma and seminoma of the testis and ovary and selected patients with extragonadal presentations. Testicular non-seminoma patients with bulky lung metastases and/or hepatic involvement are excluded.

Of eleven patients with advanced disease receiving BEP either alone or in conjunction with radiation therapy and/or surgery 10 are alive at 8–22 months (median 16 months). One patient died of uncontrolled disease at 14 months and two are alive with evidence of disease. Preliminary experience indicates that haematological toxicity is not significantly different from the PVB regime, but gastro-intestinal toxicity is less. It is suggested that the lower toxicity combination may prove to be of particular value in non-seminoma patients with small-volume metastases and patients over the age of 40 years who tolerate PVB less well.

Phase I and II Studies of VP16-213 Plus Vinblastine, Bleomycin and Cis Platinum in Advanced Testicular Teratoma

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Despite greatly improved results in the chemotherapy of metastatic testicular teratoma many patients with bulky advanced disease (Marsden stages IV L_3 and IVH_+) still die. VP16-213 has produced a 43% response rate in patients relapsing after the Einhorn regime and a phase I study of this drug in combination with the Einhorn regime was started. The initial dosage schedule was Vinblastine 0.15 mg/kg i.v. days 1 and 2; Bleomycin 30 mg i.v. weekly on day 2; Platinum 20 mg/m^2/day × 5 i.v., VP16-213 100 mg/m^2/day i.v. × 5. Fourteen patients received this regime with two early deaths (one MI and one sepsis). Seven patients became febrile whilst leucopenic and required antibiotics and haematological toxicity was more pronounced than with the Einhorn regime and the dose of VP16-213 was reduced to 100 mg/m^2 daily for 3 days only. Of 24 patients treated with the lower dose regime there have been no early deaths and preliminary analysis shows reduced haematological toxicity.

Combination Chemotherapy for Advanced Malignant Teratoma

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Sixty four male and 17 female patients with advanced malignant teratoma have received a chemotherapy regimen including VP16-213 between April 1977 and March 1981. The regimen comprised: A) Day 1 Vincristine 1.0 mg/m^2; Methotrexate 300 mg/m^2: Day 2 Bleomycin 30 mg as an i.v. infusion for 48 h; and Folinic Acid 15 mg 12 h for four doses starting at 24 h. Day 4 Cis-Platinum 120 mg/m^2 with mannitol diuresis. B) VP16-213 100 mg/m^2 days 1–5; Actinomycin D 0.5 mg days 3–5; Cyclophosphamide 500 mg/m^2 day 5. C) Hydroxyurea 500 mg q.d.s. days 1 and 2; Vinblastine 5 mg/m^2 day 3; Chlorambucil 10 mg b.d. days 3–5. D) The same as Treatment A without the Cis-Platinum. The schedule of treatments was: A, A, B, C, D. Courses were then continued in sequence B, C, D, unless drug resistance developed (detected by monitoring human chorionic gonadotrophin and alpha-foetoprotein) when the inappropriate treatment schedule was omitted. Since 1. 12. 79 treatment C has been omitted because of evidence of resistance in several patients. The present sequence is therefore A, A, B, A, B, D, B, D, etc. Survival for both male and female patients is projected at 74% by life table analysis. Results of any regimen for treatment of malignant teratoma must be assessed in the light of the prognostic factors. The regimen described here has induced sustained complete remissions in some patients with adverse prognostic factors including cerebral metastases, liver metastases and very high pre-treatment tumour marker values.

A Phase II Study of VP16-213 (Etoposide) in Refractory Metastatic Breast Carcinoma

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VP16-213 is a semi-synthetic derivative of podophyllotoxin. Preclinical trials have indicated a marked schedule dependency in the L1210 system suggestive of an advantage to short-cycle times and divided dose regimens. Seventy-seven patients with advanced breast carcinoma were studied. All patients had failed conventional combination chemotherapy (median prior treatments: 23 months). All had prior Adriamycin and more than half had prior exposure to vinca alkaloids. The patients were randomly allocated to either: 1) intermittent bolus (INT): 50–70 mg/m^2/day over 1 h daily for 5 days (39 patients), or 2) infusion (INF): 50–70 mg/m^2/day as a continuous infusion for 5 days (38 patients). In the INT group, three patients were inevaluable (early death) and one was lost to follow-up. In the INF group, four patients were inevaluable (early death), two were lost to follow-up and one refused further treatments. In the INT group of 35 evaluable patients, eight (23%) had objective responses with five (14%) achieving partial remission (PR), six (17%) had stable disease (SD) and 21 (60%) had progressive disease (PD). In the INF group of 31 evaluable patients, seven (23%) had objective responses with one (3%) achieving CR and three (10%) achieving PR, five (16%) had SD and 19 (61%) had PD. Principle toxicity observed was myelosuppression, which was severe (granulocytes < 1,000) in approx. 50% with nadirs occuring at about day 12. Recovery was rarely prolonged beyond day 20. Nausea and vomiting were moderate with the INT schedule and absent with the INF. One patient in INT developed an anaphylactoid reaction requiring discontinuation of the drug. Congestive heart failure was precipitated by the fluid load in five patients on INF. VP16-213 has significant antitumor activity in refractory breast carcinoma and merits further evaluation. INF showed no advantage over the INT schedule in this study.

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