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A Phase I Trial of Continuous Infusion VP16-213 (Etoposide)*

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Summary. *Since there appears to be a schedule dose relationship for VP16-213, the current dose seeking study of 5 day continuous infusion was initiated. Patients not candidates for other treatments were started at 75 mg/m²/day × 5. Eight patients had prior chemotherapy, eight had radiotherapy plus chemotherapy and one patient had prior interferon. The median age was 53 (range 23–65) and the median performance status was 60 (range 50–90). Seventeen patients received 20 courses; two at 75 mg/m²/day, seven at 100 mg/m²/day, ten at 125 mg/m²/day, and six at 150 mg/m²/day. The major toxicity was hematologic and median WBC count nadirs (ranges) were respectively: 3.5 (2.3–4.7) × 10³/μl, 1.6 (0.2–3.4) × 10³/μl, 2.4 (0.1–3.6) × 10³/μl, 0.4 (< 0.1–0.7) 10³/μl. Platelet count nadirs were respectively: 150, 78 (20–189), 138 (26–326), 16 (9–88) × 10³/μl. The median days to WBC nadir and recovery and did not vary with dose and were 15 (9–21) and 24 (19–38) respectively. Median days to platelet count nadir were 12 (10–29) and recovery 24 (20–38) and did not vary with dose. Non-hematologic toxicities included mild nausea and vomiting, mild mucositis on six courses, diarrhea with two courses and fever during granulocytopenia during seven courses. Three patients manifested evidence of myocardial disease two with infarction and one with congestive failure during treatment. Two patients showed objective evidence of tumor regression, one patient with seminoma and one patient with renal cell carcinoma. The latter response was short. The current studies demonstrate that high dose continuous infusion VP16-213 is tolerable with acceptable toxicity using doses up to 125 mg/m²/day (625 mg/m² over 5 days).*

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Introduction

VP16-213 (etoposide) is a synthetic cogenitor of podophyllotoxin which has proven activity in animal studies and phase I and II clinical trials [1]. This agent has been established to have single agent activity against small cell carcinoma of the lung, non-Hodgkin's lymphoma, testicular carcinoma, and possibly other human tumors [1–4].

The response to VP16-213 appears to be both dose and schedule dependent, and trials in animal tumor models showed that smaller more frequent doses of epipodophyllotoxin gave greater increases in life span than large weekly doses [1, 5, 6]. Similarily with IV administration in humans, weekly doses appear to give poor results compared to daily doses for 3–5 days [1, 2]. Since extending the duration of drug administration correlates with improved response, the current phase I study of continuous infusion VP16-213 was undertaken to determine the maximally tolerated dose for VP16-213 given as a single agent alone by continuous infusion for 5 days.

Materials and Methods

Criteria for entry into this study required histological proof of a malignant disease and unresponsiveness to conventional therapy, no chemotherapy or radiotherapy for at least 4 weeks prior to entry onto study (8 weeks for drugs such as mitomycin or the nitrosoureas), and a minimum life expectancy of 6 weeks. Patients must have had a WBC > 3,500/μl, platelet count ≥ 100,000/μl in addition to normal hepatic and renal functions. Measurable disease was not required. Written informed consent was obtained from each patient. Baseline studies before treatment included complete blood counts and differential, urinalysis, serum electrolytes, glucose, blood urea nitrogen, calcium, phosphorus, uric acid, creatinine, bilirubin, albumin, total protein, alkaline phosphatase, serum glutamic, oxallo acetic transaminase, lactic dehydrogenase, and coagulation profile including prothrombin, partial thrombo-

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plastic time and fibrinogen. Roentgenograms, isotopic scans, and disease measurements were obtained as appropriate. During therapy complete blood counts and platelet counts were repeated weekly.

VP16-213 was supplied by the Investigational Drug Branch of the National Cancer Institute in ampules containing 100 mg/5 mls. One third of the calculated daily dose was diluted into 500 ml of physiological saline for administration over an 8-h period. Each 8-h infusion bottle was prepared fresh prior to administration. In this study, the continuous infusion rate was maintained by a controlled rate pump (IVAC, San Diego, CA, USA). Patients received continuous infusion VP16-213 as in patients in a single course of treatment which consisted of a 5 day infusion. Courses were repeated every 3 or more weeks as counts permitted. The initial dose (75 mg/m^2/day) was based on the available data from the continuous infusion study by Schell et al. in refractory metastatic breast carcinoma [7]. At least two patients were treated at each non-toxic dose level and observed for 2 weeks before patients were treated at a higher escalation dose. At least five patients were treated at any level at which reversible toxicity was observed.

Results

Patient Characteristics. Seventeen patients received 20 courses of chemotherapy at four dose levels. Patient characteristics are shown in Table 1. All courses and all patients were evaluable for toxicity. All patients had received appropriate prior therapy. Eight of the 17 had received intensive prior combination chemotherapy and an additional eight had received radiotherapy plus intensive chemotherapy. One patient with pancreatic carcinoma had been treated only with interferon prior to entry onto this protocol. Among the patients with small cell carcinoma of the lung, two of the three had received lower intermittent doses of VP16-213 as part of a combination chemotherapy regimen. Ten of the 17 patients were evaluable for response. Seven patients either had no measurable disease (6) or died prior to an observation of antitumor response (1).

Table 1. Patient characteristics for phase I continuous infusion VP16-213

No. on study	17
No. evaluable for toxicity	17
No evaluable for response	10
Median age	53
(Range)	(26-65)
Male/female	7/10
Median performance status	60
(Range)	(50-90)
Prior therapy	
Chemotherapy	8
Chemotherapy + radiotherapy	8
Interferon	1
Tumor types	
Lung – small cell	3[a]
Lung – non-small cell	1
Colon	2
Sarcoma (soft tissue)	2
Uterine carcinoma	2
Others[b]	7

[a] Two of these three patients received lower intermittent doses previously

[b] Includes one each of seminoma, renal cell carcinoma, breast carcinoma, basal cell carcinoma, squamous carcinoma of larynx, pancreatic adenocarcinoma, and ovarian adenocarcinoma

Hematologic Toxicity. All 17 patients and 20 courses are evaluable for hematologic toxicity which is tabulated according to dose level in Table 2. Dose related and dose limiting toxicity, myelosuppression, was mild at the second and third (100 and 125 mg/m^2/day) dose level respectively but was severe and occurred in all patients at the 150 mg/m^2/day dose level. At all dose levels the days to nadir generally occurred by day 15 and recovery was generally complete by the 4th week. Platelet count suppression was severe at 150 mg/m^2 and required prophylactic platelet support in five of the six patients. One patient had hemorrhagic episodes during thrombocytopenia which were corrected with transfusion. One patient with laryngeal carcinoma died toxic with progressive disease on day 16 after the white count and platelet nadirs had occurred. Of note, the nadir at 100 mg/m^2 appears to be lower than that at the next higher dose, however, three of the five patients had been extensively previously treated with combination chemotherapy and it was thus felt that the nadir was falsely low. The thrombocytopenia and leukopenia observed did not appear to be cumulative. The majority of patients received combination chemotherapy prior to entry onto this phase I study and there was no apparent increased toxicity among those patients who received radiotherapy in addition to the chemotherapy. Thus, it is not possible to determine if these modalities predisposed to myelosuppression with the VP16-213 infusion. Four patients received prior nitrosoureas and all had WBC nadirs below 1,000/μl and platelet count nadirs below 100,000/μl. Thus, these patients may account for some of the increased toxicity observed at the 100 mg/m^2 dose level.

Non-hematologic Toxicity. All non-hematologic toxicity, except for cardiac toxicity (see below), was mild and easily tolerated. Four courses were associated with nausea and vomiting which was mild and easily reversible with antiemetics. Six patients developed mild (grade 1 of 4) mucositis which spontaneously cleared. Three courses were associated with diarrhea and seven courses were associated with fever during granulocytopenia requiring systemic empiric antibiotics. One patient died of infection during a period of granulocytopenia. Non-hematologic toxicity according to dose is listed in Table 3. Alopecia was not

Table 2. Hematologic toxicity for continuous infusion VP16-213: phase I

Dose (mg/m^2/day × 5)	No. patients/ no. courses	Median WBC nadir × $10^3/\mu l$	Median days to WBC nadir	Median days to WBC recovery	Median platelet nadir × 10^3	Median days platelet nadir	Median days platelet recovery
75	2/2	3.5 (2.3–4.7)[a]	16 (13–20)	20	150	–	–
100	5/7	1.6 (0.2–3.4)	15 (11–21)	28 (19–38)	78 (20–189)	12 (10–15)	29 (21–38)
125	7/10	2.4 (0.1–3.6)	16 (10–21)	25 (20–31)	138 (26–326)	14 (10–29)	22 (20–25)
150	6/6	0.3 (0.1–0.7)[b]	12 (9–16)	24 (20–28)	16 (9–88)	12 (9–16)	24 (20–28)[b]

[a] Indicates ranges
[b] Includes one toxic death after count nadirs

Table 3. Non-hematologic toxicity from phase I continuous infusion VP16-213

Type	Dose (mg/m^2/day × 5)			
	75	100	125	150
Nausea and vomiting	0	1	2	3
Mucositis (mild)	0	0	2	4
Diarrhea	0	1	0	2
Fever/granulocytopenia	0	0	2	5
Cardiac[a]	0	1[b]	1[c]	1[d]

[a] All patients "cardiotoxicity" had pre-existing cardiovascular disease
[b] One patient had anteroseptal infarction
[c] Patient developed congestive failure and expired on day 8
[d] Patient developed anteroseptal infarction on day 4 of course 2

evaluable because all but one patients had received prior chemotherapy and had alopecia prior to initiating the VP16-213.

Cardiac Toxicity. Three of eight patients with preexisting cardiovascular disease developed evidence of cardiac disorders presumed to be cardiac toxicity in association of VP16-213 infusion. Two developed anteroseptal myocardial infarctions, one at the 100 mg/m^2/day dose level and one at the 150 mg/m^2/day dose level. The latter patient developed the myocardial infarction on day 4 of the second course. Both patients had pre-existing coronary artery disease. One patient also developed congestive heart failure at the end of the 5 day infusion and expired from congestive failure on day 8. This latter patient was known to have coronary artery disease and had pre-existing episodes of congestive failure. This patient had received VP16 in saline as described and thus received a saline load of 1,500 ml daily for 5 days.

Therapeutic Response. Ten of the 17 patients are considered evaluable for antitumor response. Two patients had objective evidence of tumor regression greater than 50%, one patient with disseminated seminoma and one patient with renal cell carcinoma. The latter response (3 weeks) was of short duration and the tumor progressed after the second course of chemotherapy. In addition, one patient with small cell carcinoma of the lung, not previously exposed to VP16-213 was stable during the first infusion but progressed after the second infusion.

Discussion

The results of this phase I study of infusion VP16-213 indicates that the drug may be given by continuous infusion for 5 days with tolerable toxicity. The dose related and dose limiting toxicity was myelosuppression, including both leukopenia and thrombocytopenia. Other toxicities seen included: nausea and vomiting, mucositis, diarrhea, fever during period of granulocytopenia, and cardiac toxicity among patients with pre-existing cardiovascular disease.

Although myelosuppression was seen at the 100 mg/m^2/day dose level, there were an excess of patients previously treated with nitrosoureas and it was felt that higher dose escalations could be made. Hematologic toxicity at the 125 mg/m^2 dose level were considered acceptable, however, all patients receiving 150 mg/m^2/day experienced severe myelosuppression.

Three of eight patients with pre-existing cardiovascular disease experienced evidence of acute cardiac toxicity suggesting that VP16-213 by continuous infusion must be administered cautiously to patients with underlying cardiovascular disease. The saline load (1,500 ml/24 h) was excessive for the patient with a history of previous congestive heart failure.

The animal and human data suggest that increasing the duration of VP16-213 exposure may improve response [1–6]. Therefore further trials utilizing continuous infusion VP16-213 appear warranted. Pharmacokinetics obtained during continuous infusion by D'Incalci et al. [8] indicate that steady state levels of 3–5 μg/ml in plasma can be achieved with doses of 100 mg/m^2/24 h. Further pharmacokinetic studies to delineate the free VP16-213 as opposed to the protein bound moeity are indicated for future continuous infusion trials. The current study suggests that a dose of 125 mg/m^2/day for 5 days can be used as a safe dose for future trials which might prospectively compare continuous infusion with intermittent dose administration.

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