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Phase II Trial of VP16-213 in Non-small Cell Lung Cancer (NSCLC)*, **

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Summary. *Fifty-one patients with non-small cell lung cancer (NSCLC) were treated, during a phase II trial, with 4'demethylepipodophyllotoxin-β-D-ethylidene glucoside (VP16-213). Forty-nine were evaluable for response, and of these two (4%) had partial responses lasting 5 and 6 months. Prior treatment with chemotherapy may have adversely affected response rate; none of the 24 previously treated patients had a major response. Myelosuppression was the dose limiting toxicity. Anorexia, nausea and vomiting, partial alopecia, and chills plus hypotension during drug infusion were the other toxic effects. We conclude that VP16-213 has only minimal activity as a single agent in NSCLC.*

Introduction

VP16-213 is a semisynthetic derivative of the plant extract podophyllotoxin [7]. It has several cytotoxic properties including induction of metaphase arrest, inhibition of nucleoside incorporation into DNA and RNA, and induction of single strand breaks in DNA [1].

Phase II studies of VP16-213 in NSCLC have employed different dosages and schedules which makes comparison of results somewhat difficult. Falkson et al. [6] treated nine patients with oral VP16-213 at 200–400 mg/day for 5 day courses which were repeated at 14 or 21 day intervals. He noted one partial response. Nissen et al. [9] treated 60 patients with NSCLC with twice weekly intravenous VP16-213 given at three dosage levels: 60, 90, and 135 mg/m^2/dose. Two (3%) major responses were noted. Eagan et al. [4] conducted a trial in which 44 patients with measurable or evaluable NSCLC were treated with 140 mg/m^2 of VP16-213 on days 1, 3, and 5 every 4–5 weeks. An 18% overall tumor regression rate was achieved.

In an attempt to further define the single agent activity of VP16-213 in NSCLC a phase II trial was conducted at the Memorial Sloan-Kettering Cancer Center. This paper reports the results of that trial.

Patients and Methods

Fifty-one patients with NSCLC were treated with VP16-213 from May 1980 to January 1981. All patients had histologically proven NSCLC, with the diagnosis confirmed by the Department of Pathology at the Memorial Sloan-Kettering Cancer Center, New York, USA. All patients had bidimensionally measurable disease. Forty-four patients had adenocarcinoma, and seven had epidermoid carcinoma. Patient characteristics are summarized in Table 1. Requirements for entry into the study included a WBC count of ≥ 4,000/mm^3, a platelet count of ≥ 120,000/mm^2, and a Karnofsky

Table 1. Patient characteristics

Patients	
Entered	51
Evaluable	49
Performance status, median (range)	80 (50–90)
Prior chemotherapy	24
No prior chemotherapy	25
Adenocarcinoma	42 (86%)
Epidermoid carcinoma	7 (14%)
Age, median (range)	59 (32–79)

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performance status of ≥ 50%. Informed consent was obtained from all patients prior to entry into the study.

Pretreatment evaluation consisted of a complete history and physical examination, and a laboratory evaluation which included a complete blood (CBC), 12-channel biochemical screening profile, serum creatinine, and a chest roentenogram. Radionuclide studies of bone and liver were done only when clinically indicated. All patients had a physical examination and a CBC at least every 3 weeks; an additional CBC was performed 10 days after starting each course to document blood count nadir. Chest roentenograms and biochemical screening profiles were obtained every 4–6 weeks unless clinically indicated at closer intervals.

VP16-213 was administered every 3 weeks on days 1, 3, and 5 as a slow intravenous infusion (45 min). The starting dose was 120 mg/m^2 (PS ≤ 70) or 150 mg/m^2 (PS > 70) (total initial dose: 360–450 mg/m^2/course). In the absence of myelotoxicity the dosage was escalated by 20 mg/m^2/dose every second course of treatment until myelosuppression was observed. The highest dose level achieved in any patient was 200 mg/m^2. If significant myelosuppression was present, at the time a patient was due to begin a new course of treatment (WBC < 3,000/mm^3 or platelets < 100,000), doses were decreased by 20 mg/m^2 or withheld until the patient recovered. After two courses of three doses each, patients were evaluated for response; one full course was necessary to be considered evaluable for response.

Definitions of response were as follows: Complete response – disappearance of all evidence of disease for at least 1 month; partial response (PR) – ≥ 50% but less than 100% reduction in the product of the two longest perpendicular diameters of all measurable lesions for at least 1 month; minor response (MR) – ≥ 25% reduction in the products of the two longest perpendicular diameters but less than required for PR; and progression – increase in size of any lesions or appearance of additional lesions.

Results

Forty-nine of the fifty-one patients entered into this study were evaluable for response. One of those inevaluable for response was found not to have primary lung cancer, and the other was a major protocol-violation. Two patients had partial responses lasting 5 and 6 months. Responses in both patients occurred in pulmonary parenchymal lesions. One responding patient had adenocarcinoma, and the other epidermoid carcinoma. There were two minor responses in previously untreated patients lasting 3 and 4 months, and three minor responses in previously treated patients lasting 1, 4, and 5 months. Among the remaining 42 patients, eight had stable disease for 2–5 months; the other 34 patients had progressive disease. Responses are summarized in Table 2.

Prior treatment with chemotherapy may have had a negative effect on attaining a major response. Both PR's occurred in the previously untreated group, whereas there were no major responders among the 24 patients who had previously received chemotherapy. A partial response in each patient was associated with ≥ 20% improvement in performance status.

Table 2. Responses

Evaluable	49
CR	0
PR (months)	2 (5, 6)
MR	5
Prior chemotherapy	0/24 PR
No prior chemotherapy	2/25 PR

Toxicity

The median number of courses of treatment per patient was 3 (range 1–8). Myelosuppression was both the dose limiting, and most common toxicity; median lowest WBC nadir was 3.9 (range 0.0–10.4), median platelet nadir was 198,000 (range 19,000–454,000). There were two drug related deaths, both in patients with septicemia and WBC's ≤ 1,000/mm^3.

Other side effects included anorexia, nausea and vomiting, and partial alopecia. One patient experienced chills and hypotension during infusion of VP16-213. These symptoms resolved spontaneously and rapidly upon discontinuation of the drug infusion. The patient received subsequent doses, after pretreatment with steroids and diphenhydramine, without untoward effects.

Discussion

Recently, several trials have been undertaken to evaluate VP16-213 as a component of polydrug chemotherapy in the treatment of NSCLC. Cavalli et al. [3] noted a 16% response rate with a combination of cyclophosphamide, methotrexate, vincristine, and VP16-213. In that trial toxicity necessitated administering substantially less than the planned dosage of each of the drugs. Eagan et al. [5] added VP16-213 to their regimen of cytoxan, adriamycin, and cisplatin in adenocarcinoma of the lung and noted a 35% response rate. In two trials employing cisplatin plus VP16-213 response rates of 31% and 41% were noted respectively [2, 8].

Using maximally tolerated doses we noted an overall response rate of 4%. No patient with prior treatment with chemotherapy had a major response, and there were no complete responders. We conclude that VP16-213 has only minimal activity as a single agent in NSCLC.

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