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Epipodophyllotoxin (VP16-213) in Small Cell Carcinoma of the Bronchus Resistant to Initial Combination Chemotherapy

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Summary. *Thirty-eight patients with small cell carcinoma of the bronchus resistant to initial chemotherapy with cyclophosphamide methotrexate and CCNU, were treated with VP16-213 alone in a dose of 120 mg/m² i.v. on days 1, 3, and 5 every 3 weeks. Twelve patients died before three courses of treatment. In 26 patients who received three or more courses only one, transient partial response occurred. One or more components of the initial chemotherapy seems to confer resistance to the action of VP16-213 in this disease.*

Introduction

VP16-213 has been shown to produce regressions in small cell carcinoma of the bronchus (SCCB) [1]. Used as a single agent the responses are seen in approximately 50% of patients with previously untreated disease [3, 6]. There is very little information about the effect of previous chemotherapy on response to VP16-213, although other studies have suggested lack of cross resistance to other drugs [2, 4, 5] which, if true, would add to its usefulness. As part of a study of treatment with chemotherapy alone we have assessed the effect of VP16-213 on patients with SCCB who were resistant to initial chemotherapy or who had relapsed following treatment.

Patients and Methods

Ninety-eight consecutive, previously untreated patients with SCCB were treated with chemotherapy. All patients had a histologically or cytologically proven diagnosis. The extent of disease was determined by chest x ray, full blood count, isotope scans of bone, brain and liver, liver function tests and marrow aspiration and biopsy. The initial chemotherapy regimen (CMC) consisted of 3 weekly courses of Cyclophosphamide 1 g/m²/i.v. reducing to 750 mg/m² on courses 3 and thereafter, methotrexate 200 mg/m² by infusion over 24 h with folinic acid rescue at 27 h in each cycle and CCNU 100 mg/m²/p.o., on cycles 1 and 3 only. Treatment was continued until relapse occurred or was discontinued at 2 years.

In 38 consecutive patients VP16-213 was used as the sole treatment for relapse or for failure of response to initial treatment. The drug was given i.v. as a 30 min infusion at a dose of 120 mg/m² on days 1, 3, and 5 of a 21 day cycle. Treatment was continued until there was further progression of disease following which palliative treatment was given only.

All 38 patients starting VP16-213 were ambulant and judged capable of completing three courses or more of further chemotherapy. Therapy was initiated in all on an out patient basis.

Complete response meant disappearance of all tumour. A partial response (PR) was a reduction in size by at least 50% of the greatest diameter in all measurable lesions. Any response less than this or which could not be evaluated was termed no response (NR).

Results

In 12 patients less than three cycles of treatment were given before death from the tumour. None of these showed a PR transiently. In 26 patients three or more cycles of VP16-213 were given. The response to the initial chemotherapy in the 26 patients was CR in four, PR in 13, and NR in nine.

Of the 26 patients who received three or more cycles of VP16-213, 15 showed disease progression or no improvement after three courses, and 10 showed either no improvement or a transient response and received between four and 12 courses before relapse occurred. In only one case could the response be called a partial response.

Toxicity

VP16-213 was well tolerated following the initial chemotherapy. A total of seven cycles of treatment were delayed by 1 week due to asymptomatic

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neutropenia. Mild nausea was frequent and alopecia occurred in all patients but there were no other toxic effects.

Survival

The median survival from the time of first relapse in all patients on CMC was 84 days. During the period of study when no VP16-213 was available 60 patients relapsed with a median survival of 75 days. The 38 patients treated with VP16-213 had a median survival of 126 days.

Discussion

These disappointing results clearly show that VP16-213 is ineffective following treatment with the unrelated agents cyclophosphamide, methotrexate and CCNU. The reported response rates to VP16-213 in untreated SCCB are in the region of 50% [3], which means that our poor results in 38 patients are unlikely to be due to chance.

Other studies have produced better results than ours. Cohen et al. [2] reported on 16 patients who had been previously treated with CMC and other agents. Four of the 16 showed a PR of 60–204 days duration. They used a different regimen with VP16-213 being given at a dose of 200 or 300 mg/m^2 weekly. Jansen et al. [4] also achieved a 50% partial response rate in 28 patients previously treated with CMC. The dosage was 130 mg/m^2 daily orally for 5 days every 3 weeks. On the other hand Nissen et al. [5] reported on 20 patients refractory to other treatment (unspecified) where VP16-213 produced a response rate of only 10%. The dose used is unclear but the schedule was twice weekly.

The dose which we have used seems adequate as judged by other studies [1] so underdosage does not seem to be an adequate explanation for our results. The criteria for response which we have used are widely adopted. There may however be some activity of the drug not recorded by response rate since the patients treated with three or more cycles of VP16-213 lived longer than those treated palliatively after relapse on CMC. It seems more likely however that treatment with one or more components of CMC does confer resistance to the effect of VP16-213 in spite of earlier reports to the contrary. This finding is of course similar to that found with other drugs in other cancers.

References

1. Arnold AM (1979) Podophyllotoxin derivative VP16-213. Cancer Chemother Pharmacol 3: 71
2. Cohen MH, Broder LE, Fossieck BE, Ihde DC (1977) Phase II clinical trial of weekly administration of VP16-213 in small cell bronchogenic carcinoma. Cancer Treat Rep 61: 489
3. 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
4. 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 (NSC 141540, 4′-demethylepipodophyllotoxin 9-(4,6-o-thylidene-β-D-glucopyranoside). Cancer 40: 633
5. 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 diseasse. Cancer 45: 232
6. Tucker RD, Ferguson A, Van Wyck C, Sealy R, Hewitson R, Levin W, Rad FF (1978) Chemotherapy of small cell carcinoma of the lung with VP16-213. Cancer 41: 1710

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