

Oral VP-16-213 in advanced bronchogenic carcinoma and toxic effects when combined with methotrexate

G ANDERSON, F BOWYER, AND L WILLIAMS

From Newport Chest Clinic, Newport, Gwent

ABSTRACT Forty-six patients with histologically confirmed lung cancer received treatment with the cytotoxic drug VP-16-213 in a dose of 100 mg twice daily, given orally for five days. The overall objective response rate was 11 out of 46 (24%) or 11 of the 33 (33%) who survived to receive two cycles. The drug was effective in all histological types. Only one patient developed leucopenia. This demonstration of the safety of VP-16-213 and its effectiveness suggested that this drug might be used in combination chemotherapy. A series of pilot studies showed unexplained marrow toxicity when VP-16-213 combined with vincristine was given with either methotrexate or adriamycin.

VP-16-213 (4'-demethylepipodophyllotoxin 9-(4, 6-O-ethylidene-B-D-glucopyranoside) is a semisynthetic podophyllin derivative reported to show activity in small cell carcinoma of the bronchus.^{1 2} We report a study of the activity of oral VP-16-213 in a variety of cell types of bronchogenic cancer.

Patients and methods

Forty-six patients with advanced histologically confirmed lung cancer were studied. Cell types were squamous carcinoma (19 cases), small cell carcinoma (10 cases), adenocarcinoma (six cases), undifferentiated carcinoma (11 cases). The term undifferentiated carcinoma was used when precise classification was not possible. The extent of disease was defined by clinical and radiological examinations. Radioisotope organ scans were only performed if there was clinical or biochemical evidence of metastases. Routine measurements were made before treatment, and before each cycle, of haemoglobin, white cell and platelet counts, blood urea, liver function tests, and chest radiograph with the appropriate lateral view. Performance status was assessed using the Karnofsky scale.³

The sites of metastases are shown in table 1. Before treatment and before each cycle measurements were made of the tumour and its metastases

and the following criteria were observed for an objective remission: complete remission (CR), complete disappearance of all measurable lesions with normal biochemical measurements for a minimum of six weeks: partial remission (PR), a decrease in 50% or more for a minimum of six weeks in the product of two perpendicular diameters of all measurable lesions. All patients had measurable lesions either of the primary tumour or of the metastases. Upon relapse other cytotoxic agents were not used.

VP-16-213 was given in gelatine covered capsules 100 mg twice daily for five days. Cycles were given at 28-day intervals indefinitely, except where disease progressed after three cycles when treatment was stopped. Patients were seen as day-patients on day 1 of each cycle. The same dosage schedule was given to 11 patients who had previously received radiotherapy and three who had failed to respond to treatment with a combination of adriamycin, 5-fluorouracil, and methotrexate.

Table 1 Sites of metastases in 46 patients

Site	Number
Mediastinum	16
Extrathoracic nodes	12
Pleura	13
Liver	9
Skin	9
Other sites	10

Twenty patients had "limited" disease (confined to lung \pm pleura \pm ipsilateral neck nodes).

Twenty-six patients had more extensive disease.

Address for reprint requests: Dr G Anderson, Newport Chest Clinic, 129 Stow Hill, Newport, Gwent.

Results

The results are summarised in table 2. The overall objective response rate (CR+PR) was 11 out of 46 (24%). Thirteen patients died before receiving a second cycle and these died as a result of their advanced disease and not of treatment, so that 11 of 33 (33%) surviving to cycle 2 showed an objective response. Responders survived a median of 34 weeks, and non-responders a median of 10 weeks. Patients received a mean of 3.8 cycles—7.6 cycles for responders and 2.7 for non-responders. One patient who is still alive and responding received a maximum of 14 cycles. Activity was shown (table 2) in all cell types. Response was seen in two of the three patients previously unresponsive to a combination of adriamycin, 5-fluorouracil, and methotrexate. In the 11 patients showing an objective response the Karnofsky status improved in nine. In those failing to respond the Karnofsky status declined but it is impossible to know whether the chemotherapy caused a more rapid decline than would have occurred if no treatment had been given.

The side-effects are shown in table 3. Only one patient developed a white cell count $<3 \times 10^9/l$ with a level of $1.8 \times 10^9/l$. Six became anaemic, $Hb < 10.0$ g/dl (10.0 g/l). This occurred in all between cycles 4 and 5 in patients showing a poor response and was probably caused by the disease rather than the treatment. Some degree of alopecia was invariable and was often complete. Gastrointestinal intolerance was never severe and a single confused patient developed transient blindness which resolved completely.

Table 2 Results of treatment

Cell type	Number starting treatment	Number surviving to cycle 2	Objective remission
Squamous	19	12	4 (CR1, PR3)
Undifferentiated	11	8	2 (CR1, PR1)
Small cell	10	8	3 (CR0, PR3)
Adenocarcinoma	6	5	2 (CR0, PR2)
Total	46	33	11 (CR2, PR9)

CR=complete remission; PR=partial remission.

Table 3 Side-effects in 46 patients

Side-effect	Number
Nausea	4
Dysphagia	2
Diarrhoea	1
Anaemia ($Hb < 10.0$ g/dl)	5
Leucopenia ($WBC < 3 \times 10^9/l$)	1
Transient blindness	1

Discussion

These results confirm that VP-16-213 is an effective agent in treating lung cancer. Cavalli *et al*¹ gave oral VP-16-213 in drinking ampoule form in a total dose of 850 mg/m² over three days and claimed remission (CR or PR) in eight of 19 patients (42%) with small cell carcinomas. The mean white cell count nadir of $2.3 \times 10^9/l$ occurred around 10–14 days. Hansen *et al*² gave the same preparation of VP-16-213 in a dose of 800 mg over four days or 1000 mg over five days and obtained objective remission in 20 of 40 patients with small cell carcinomas. Twenty-four developed a white cell count $<3 \times 10^9/l$.

The present study was designed to assess the effects and toxicity of VP-16-213 in all cell types of lung cancer. The group studied had very widespread disease and the overall response rate is probably best judged as 11 of the 33 patients surviving to receive cycle 2. In addition to its effect in small cell carcinomas VP-16-213 is also effective in the other cell types against which its effect has not previously been tested. An impressive feature was the low level of haematological toxicity, especially considering that 14 patients had previously received radiotherapy or other forms of chemotherapy. We may have underestimated the incidence of leucopenia and thrombocytopenia by measuring blood counts before the next cycle (28 days) rather than at the nadir (10–14 days) but this seems justified as it is the count before the next cycle which determines whether to proceed with chemotherapy. Certainly, there was no evidence of progressive marrow depression. The gastrointestinal toxicity was mild and this form of chemotherapy was acceptable to patients.

Addendum

The demonstration that oral VP-16-213 showed effectiveness and low toxicity led to three subsequent pilot studies, all of which were abandoned because of unexplained marrow toxicity. Schedule A consisted of oral VP-16-213, 200 mg orally days 1 to 5, vincristine 2 mg iv, on day 1 and methotrexate 300 mg iv on day 1, followed 24 hours later by oral leucovorin 15 mg six hourly for six doses. Schedule B used the same doses of VP-16-213 and vincristine but only 100 mg of methotrexate iv on day 1 and folinic acid rescue was extended to 10 mg orally six hourly for nine doses starting at 24 hours. Schedule C used the same doses of VP-16-213 and vincristine with a small dose of adriamycin (20 mg/m² iv on day 1).

Two of eight patients receiving schedule A developed a profound pancytopenia and one died. Two of eight receiving schedule B developed a pancytopenia, one after two cycles and the other with a single cycle. One of this group died of an *E coli* septicaemia and the other recovered. One of five patients on schedule C died of pancytopenia after a single cycle. All these patients had normal levels of blood urea, were well hydrated and none failed to take the folinic acid rescue.

This interaction on the marrow is unexplained. Vincristine has little depressant effect on the bone marrow nor has methotrexate in the doses used in schedules A and B. Possibly VP-16-213 has a toxic effect on the rapidly dividing cells of the intestinal villi, thus blocking the absorption of the orally administered folinic acid. Three of four patients showing marrow toxicity on schedules A and B had pleural or pericardial effusion, and it is possible to speculate that these effusions acted as "sponges" which absorbed methotrexate which was subsequently released after completion of folinic acid rescue. Neither theory explains marrow depression with schedule C which did not contain methotrexate.

We suggest that while VP-16-213 is a highly effective drug in bronchogenic carcinoma it should be used with caution in drug combinations, especially with those containing methotrexate.

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References

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