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VP16-213 as a Single Agent in Advanced Testicular Tumors

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Abstract—*Twenty-six patients with metastatic testicular tumours* (25 *teratoma*, 1 *seminoma*) *were treated with VP*16–213 *as a single agent. Two dose schedules were used*—120 mg/m^2 *i.v. daily for* 5 days, *repeated after* 2–4 weeks (20 *patients*) *and* 100 mg/m^2 *i.v. daily for* 5 days, *repeated after* 4 weeks (6 *patients*). *Twenty-four patients were assessable for tumour response. Most patients received at least* 2 *courses of treatment. Three patients* (12.5%) *with malignant teratoma achieved complete remissions and all remain in remission at* 52, 40 *and* 32 weeks. *The response rate was* 46% (*complete* 12.5%, *partial* 33.5%) *with an additional* 8% *showing clinical improvement. Toxicity was reversible and usually not severe, but there was one drug-associated death. The major side effects were neutropenia and thrombocytopenia. VP*16-213 *has activity in testicular teratoma comparable with that of other first line agents and should repay evaluation in combination.*

INTRODUCTION

VP16-213 (NSC 141540) is a semisynthetic epipodophyllotoxin derivative which acts *in vitro* by preventing cells from entering mitosis or by destroying them in the premitotic phase [1, 2]. The compound has antitumour activity in acute non-lymphoblastic leukaemia, Hodgkin's and non-Hodgkin's lymphoma and in some solid tumours, notably small cell carcinoma of the lung [3–7]. Modern combination chemotherapy is now capable of producing a prolonged complete remission rate of 65–70% in disseminated testicular cancer [8]. However, patients who achieve partial remission only (often those with large volume metastases) and those who relapse after chemotherapy still fare badly. Thus there is still a need for new effective agents which can ultimately be used in combination with established drugs like cis-platinum, vinblastine and bleomycin. Preliminary reports have suggested that VP16-213 is of value in the treatment of metastatic testicular teratoma [9–12] and for these reasons a phase II study with VP16-213 was performed. Twenty-six patients with metastatic testicular teratoma and one with metastatic seminoma have been treated in our units with VP16-213 alone and are the subject of this report.

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MATERIALS AND METHODS

Patient selection

Twenty patients at the Royal Marsden Hospital and 6 patients at the Charing Cross Hospital had histologically proven advanced malignant testicular teratoma or seminoma. Twenty-four were evaluable for tumour response. All, except 1, had received previous chemotherapy, radiotherapy or a combination of both. Metastatic resistant disease was in evidence as progressively enlarging nodal tumour (abdominal or supradiaphragmatic), as pulmonary metastases, as an elevation of serum alpha-foetoprotein (AFP) or serum beta subunit of human chrorionic gonadotrophin (β-HCG) or as some combination of these. The one patient to receive primary treatment with VP16-213 was a paraplegic, mentally retarded patient who would not have tolerated more aggressive treatment with vinblastine, bleomycin and cis-platinum [13]. Only two patients had received previous radiotherapy alone. The mean duration of previous treatment was 8.8 months (range 0–25 months). No patient had received any chem-

otherapy or radiotherapy during the 4-week period prior to the commencement of the first course of VP16-213.

Evaluation

Full clinical examination, chest and plain abdominal radiographs (following initial bipedal lymphangiography), complete blood count and liver and renal function tests were performed on all patients before the first and after each subsequent course of treatment. The serum marker proteins alpha-foetoprotein (AFP) and the beta subunit of human chroionic gonadotrophin (β-HCG) were simultaneously serially measured. Computerized axial tomographic scanning of the lungs was performed in 2 cases.

Treatment schedule

Two schemes were used. At the Royal Marsden Hospital VP16-213 was given to 20 patients in a dose of 120 mg/m^2 (maximum dose 200 mg) daily as an i.v. infusion for 5 consecutive days every 2–4 weeks. The drug was diluted with 200 ml N saline and was infused over 20–30 min. The schedule used for the Charing Cross Hospital patients was 100 mg/m^2 i.v. daily for 5 consecutive days and the drug was given to 6 patients in the same manner. Most patients received treatment at 4-weekly intervals. In the Royal Marsden Hospital group, treatment with VP16-213 was continued until evidence of non response or to a maximum number of 6 courses in those who responded. In non responders, at least 2 courses were given before it was concluded that VP16-213 was of no benefit. The 6 Charing Cross Hospital patients received between 1 and 3 courses of VP16-213 each before proceeding to combination regimens which included VP16-213 in those patients whose tumours had responded. One patient (case 4, Table 1) also received one oral course of VP16-213 (600 mg/day for 5 consecutive days). No specific dosage modification scheme was adopted but further courses of VP16-213 were not given until peripheral blood white cell and platelet counts had returned to the normal range.

Criteria for response

Complete response (CR) was defined as the disappearance of all clinical and radiological evidence of active disease for at least 4 weeks, with a fall in AFP and/or β-HCG to the normal range, if either or both of these markers had been elevated.

Partial response (PR) was defined clinically as a greater than 50% decrease in the sum of the products of the largest perpendicular diameters of all measurable lesions, lasting at least 4 weeks, with no new lesions appearing. For those patients monitored by tumour markers, partial response was defined as at least a one log fall or fall to normal range of either or both tumour markers, lasting at least 4 weeks, either with regression of, or no progression of other measurable disease, if present.

Improvement (IMP) was defined as a less than 50% reduction in the sum of the products of the largest perpendicular diameters of all measurable lesions, lasting at least 4 weeks, with no new lesions appearing and no increase in level of marker protein occurring over the same time interval.

RESULTS

Of the 26 patients studied, 24 were evaluable for tumour response and 25 were evaluable for drug toxicity. No patient died within 4 weeks of commencing treatment. Of the 2 patients not assessable for tumour response, one had no measurable disease at the time of treatment but was given VP16-213 as an adjuvant while recovering from bleomycin induced lung toxicity. The other patient had a minimal elevation of AFP as the only evidence of active disease and, while this returned to the normal range after 1 course of VP16-213, this result is not considered significant. Both of these patients have been excluded from the tumour response analysis. The total number of courses given of VP16-213 was 70 (including 1 oral) with a mean of 2.7 courses per patient. Three patients achieved CR (12.5%) and 8 achieved PR, giving a response rate of 46%. Two other patients showed improvement so that, overall, 13 patients (54%) showed benefit. One patient showed a fall to the normal range of AFP but simultaneously developed lung metastases after 2 courses of treatment. He is not considered to have shown a response. Only 10 patients are assessable for duration of response (Royal Marsden Hospital group). The mean duration of response at the time of reporting is 24.9 weeks (range 4–68 weeks), with 3 patients still remaining in complete remission 52, 40 and 32 weeks, respectively, after cessation of treatment (Table 1). An additional patient who has been excluded from this analysis because

Table 1. *Details of* 13 *patients showing response to VP*16-213

Patient and histological subtype	Previous treatment	Response to VP16-213			
		Clinical and radiological	AFP	β-HCG	Duration (weeks)
1 MTI	6 courses vinblastine + bleomycin*	NA	↓PR	NR	12
2 MTU	6 courses vinblastine + bleomycin*	CR	NE	NE	40†
3 MTI/YS	4500 rad to para-aortic and bilateral pelvic nodes	IMP	NE	NE	4_a
4 MTI	4 courses vinblastine + bleomycin* 4000 rad to 3rd, 4th and 5th lumbar vertebrae	IMP	↓PR	↓PR	16
5 S	Radiotherapy to abdominal, pelvic, mediastinal, supraclavicular and axillary nodes	IMP	NE	NE	4
6 MTT	2 courses vinblastine + bleomycin*	NR	NE	↓PR	68
7 MTU	4000 rad to para-aortic nodes and ipsilateral pelvic nodes 2 courses vinblastine + bleomycin,* vinblastine, cis-platinum, adriamycin, DTIC, cyclophosphamide, actinomycin D, ifosphamide, vindesine	NR	↓PR	1 log	7
8 MTU	Radiotherapy to para-aortic, pelvic, and supraclavicular nodes Cyclophosphamide, 5 courses vinblastine + bleomycin,* actinomycin-D, methotrexate and folinic acid rescue, cis-platinum	CR	↓	NE	52†
9 MTU	6 courses vinblastine + bleomycin*	CR	NE	NE	32†
10 MTT/S	None	NR	NE	1 log	10
11 MTU/S	4 courses vinblastine + bleomycin* 2 courses vinblastine, bleomycin + cis-platinum	NR	↓PR	NE	8
12 MTI‡	4200 rad to para-aortic and bilateral pelvic nodes Hydroxyurea, vincristine, methotrexate, cyclosphosphamide, actinomycin D, adriamycin, melphalan, cis-platinum	IMP	NE	1 log PR	—
13 MTT‡	Vincristine, methotrexate, bleomycin, cyclophosphamide, actinomycin D, chlorambucil	IMP	NR	1 log PR	—

*Vinblastine 15 mg i.v. on days 1 and 2 and bleomycin 30 mg i.v. as a 24-hr infusion on days 1, 2, 3, 4 and 5.
†Continued remission at time of analysis.
‡Charing Cross Hospital patient.
CR Complete response.
PR Partial response.
NR No response.
NA No assessable disease.
IMP Improvement.
NE Not elevated before treatment with VP16-213.
↓ Elevated pre-treatment marker which fell to normal range with treatment.
1 log At least 90% fall from pre-treatment value, but not to normal range.
MTU Malignant teratoma undifferentiated.
MTI Malignant teratoma intermediate.
MTT Malignant teratoma trophoblastic.
YS Yolk sac elements.
S Seminoma.
a Chemotherapy electively changed after one course of VP16-213.

primary histology was not available, but who had presented (acutely) with extensive disease and raised β-HCG and AFP, also responded to 2 courses of VP16-213 with a greater than one log fall in β-HCG and an improvement in AFP for 4 weeks.

Toxicity

Of 25 patients evaluable for toxicity, leucopenia (WBC $< 3.0 \times 10^9/l$) and thrombocytopenia (platelets $< 100 \times 10^9/l$) occurred in 14 (leucopenia in 5 thrombocytopenia in one and both in 8). The 26th patient did not have a blood count performed until the third week following a course of VP16-213. This count was normal but it is possible that earlier myelosuppression, with recovery, was missed and he has been excluded from the toxicity analysis. The accumulated blood count toxicity data are given in Table 2. Because most patients in this series were treated on an outpatient basis, blood counts were usually done at weekly intervals. It is thus not possible to indicate precisely the day on which nadirs occurred but they were usually seen during the week following that in which treatment was given. One patient died of gastrointestinal tract haemorrhage while thrombocytopenic in the fifth week after the commencement of the first course of VP16-213. Duodenal ulceration with erosion of the gastroduodenal artery was found at autopsy. No tumour was found at this site. Nausea and vomiting occurred in one patient and one complained of muscle cramps while on treatment. Complete epilation occurred in the three patients who had not already been epilated by the previous chemotherapy.

DISCUSSION

VP16-213 has activity in malignant testicular tumours and can produce complete remission in disseminated disease when used alone. The overall CR and PR rate of 46% compares well with that for other single agents [14, 15]. The drug is well tolerated, usually causing only moderate myelosuppression and can be given to out-patients. Significant blood count depression occurred in 56% of patients. The fact that responses were seen in patients who had relapsed following previous chemotherapy demonstrates lack of cross-resistance between VP16-213 and other active agents. It remains to be seen whether the complete remissions are maintained and close follow up of these 3 patients continues. Two yr is the time interval beyond which sustained CR could be expected [15]. The 3 patients who achieved CR all had pulmonary metastases (one with an associated elevation of AFP). This may be a chance finding although the favourable response of minimal pulmonary disease to other drugs has been previously noted [8].

VP16-213 warrants further trial, in combination with other agents, in disseminated testicular teratoma and seminoma, and these studies have now begun.

Table 2. Myelotoxicity of VP16-213 (25 patients assessable)

		Haemoglobin (g/l)	White cell count ($\times 10^9/l$)	Platelet count ($\times 10^9/l$)	Mean duration of prior chemotherapy (weeks)
Royal Marsden Hospital (20 patients)	Mean nadir	110	3.5	152	
	Median nadir	115	3.6	151	18
	Range	57–140	0.1–9.6	16–454	
Charing Cross Hospital (5 patients)	Mean nadir	91	1.6	102	
	Median nadir	87	1.2	99	
	Range	53–126	0.8–3.5	13–187	58

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