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Anti-Tumour Activity of the Epipodophyllin Derivative VP16-213 (Etoposide: NSC-141540) in Gestational Choriocarcinoma

E. S. NEWLANDS and K. D. BAGSHAWE

Department of Medical Oncology, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, United Kingdom

Abstract—*We have treated a total of* 47 *patients with gestational choriocarcinoma with the epipodophyllin derivative, VP*16-213, *alone and in combination. Twenty-six out of* 31 *patients who could be clearly assessed for response had drug-resistant disease. Of these* 31 *patients the results were as follows: with VP*16-213 *alone* (100 *mg/m*^{2} *i.v. on* 5 *consecutive days) there were* 9 *responses and* 7 *improvements out of* 26 *patients. When VP*16-213 *was given in the same dose combined with methotrexate and vincristine, there was* 1 *response and* 2 *improvements out of* 4 *patients; with VP*16-213 *in the same dose given after a bleomycin infusion, the only patient that was treated with this combination responded. At present there are a total of* 11 (35%) *responses and* 9 (29%) *improvements to VP*16-213, *alone and in combination, out of* 31 *patients, producing a combined response and improvement rate of* 64%. *VP*16-213 *is clearly an active agent which requires further assessment in treating drug-resistant gestational trophoblastic tumours and patients presenting with adverse prognostic factors.*

INTRODUCTION

VP16-213 [ethylidene-β-D-glucopyranosyl epipodophyllotoxin (etoposide; NSC-141540)] is a semi-synthetic derivative of podophyllotoxin and has been shown to have activity in a number of animal tumours [1–3] and some human tumours [4–7]. The action of VP16-213 may be by inducing single-strand breaks in DNA, rather than by inhibiting the mitotic spindle formation, which is probably the main cytotoxic action of the parent podophyllotoxin compound [8, 9]. VP16-213 has been shown to have activity in acute myelomonocytic leukaemia, Hodgkin's disease and non-Hodgkin's lymphoma [4–6]. In solid tumours responses have been seen in small cell carcinoma of the lung and ovarian carcinoma [4, 7] and malignant teratomas [10–12]. Preliminary experience with VP16-213 in drug-resistant choriocarcinoma has already been reported [10, 11]. VP16-213 is a well tolerated antitumour agent which has activity in a range of human tumours.

Gestational trophoblastic tumours are initially drug-sensitive, but where there are adverse prognostic factors [13], they have frequently proved resistant to methotrexate. However, with the introduction of drug combinations which include methotrexate, vincristine, actinomycin D, cyclophosphamide, adriamycin, melphalan and 6-mercaptopurine, the incidence of disease resisting eradication has fallen to approximately 5% of cases treated at this Centre [14]. Once the tumour has become resistant to standard agents it has previously proved difficult to get further satisfactory antitumour responses. We have previously reported on the activity of high-dose cis-platinum in combination with vincristine and methotrexate in treating resistant gestational choriocarcinoma [11, 15]. The addition of cis-platinum in combination and VP16-213 as agents with activity against resistant gestational choriocarcinoma, is already

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reducing the number of patients who become completely drug resistant.

MATERIALS AND METHODS

Patient eligibility

All patients entered in this study had gestational choriocarcinoma which was resistant to chemotherapy with combinations of drugs including methotrexate, vincristine, actinomycin D, cyclophosphamide, adriamycin, melphalan, 6-mercaptopurine and hydroxyurea, or had adverse prognostic factors [13] at presentation. The age range of patients was from 20 to 53 yr. All patients had adequate bone marrow reserve, renal function and liver function.

Treatment protocol

VP16-213 was given in a dose of 100 mg/m^2 on 5 consecutive days. VP16-213 was diluted in approximately 200 ml of saline on each occasion and given as a short i.v. infusion. In those patients treated with VP16-213 in combination, the dose of vincristine was 1.0 mg/m^2 i.v. and methotrexate 300 mg/m^2 as a 12-hr infusion followed by folinic acid rescue 15 mg b.d. for four doses starting at 24 hr after the start of the methotrexate. VP16-213 was started on the same day as the vincristine and methotrexate and was given in the same dose on 5 consecutive days as described above. The only patient who received a bleomycin infusion received 15 mg of bleomycin per 24 hr for 72 hr prior to a 5-day course of VP16-213 as described above.

Patient monitoring

All patients were monitored twice weekly by radioimmunoassay specific for human chorionic gonadotrophin (hCGβ). This assay, which has been previously described [16], can detect down to 2 m i.u./ml (approximately equal to 1 ng/ml of hCGβ in serum).

Definition of response

The definition of response used in choriocarcinoma differs from the conventional solid tumour criteria, since there is a more accurate biochemical monitor of the disease in the hCGβ concentration and in only some patients are easily measurable secondaries present to provide linear measurements of disease activity. In the large experience of this Centre (over 500 patients treated up to 1978), the clinical and radiological evidence of disease activity correlates very accurately with the hCG concentrations, but these responses are slower than the biochemical changes. Responses in these patients were defined as follows:

A response. A greater than log fall in the serum hCGβ concentration following a single course of therapy with VP16-213 prior to the next course of chemotherapy.

An improvement. A greater than 50% fall in the hCGβ concentration following a single course of therapy prior to the next course of chemotherapy.

No response. No significant change in the hCGβ concentration.

Progressive disease. A rising hCGβ value following a course of chemotherapy. Only those patients who could be clearly assessed for response are included in this analysis.

A further 16 patients who were treated with VP16-213 could not be clearly assessed for response either because the hCG concentration was still falling after the prior course of chemotherapy, or the hCG was too near the limit of detection in the assay for hCGβ. None of the patients excluded from this analysis had stable or progressive disease.

RESULTS

The details of the 26 patients who could be clearly assessed for response to VP16-213 alone are summarised in Table 1. There were 9 (35%) responders and 7 (27%) improvements out of 26 patients. This produces a combined response and improvement rate of 62%. When VP16-213 was combined with methotrexate and vincristine, there was 1 response and 2 improvements out of 4 patients. One patient received VP16-213 following a bleomycin infusion and responded (Table 2). When added together this gives a total of 11 (35%) responses and 9 (29%) improvements out of 31 patients.

The non-haematological toxicity of VP16-213 alone and in combination was mild. Temporary alopecia occurred in some of the patients that could be assessed for this side effect. No hypotension, peripheral neuropathy, nephrotoxicity or hepatotoxicity was observed.

Haematological toxicity was moderate and reversible over a period of 10–20 days. Myelosuppression involved both leucopaenia and thrombocytopaenia, and the results are summarised in Table 3. No major complications of the myelosuppression were seen, possibly as this drug, when given in this

Table 1. Patient characteristics and results

Patient	Major site(s) of disease	HCG conc. (mi.u./ml) at start of VP16-213	HCG conc. (mi.u./ml) at start of next treatment	Response to VP16-213	Final outcome of all therapy
VP16-213 alone (previous chemotherapy)					
1. M.R	Lungs	3400	3800	Progressive disease	Died
2. A.Y	Unknown	33,000	28	Response	Died
3. A.O'M	Pelvis, lungs	380	110	Improvement	Died
4. A.Z	Lungs	95	Undetectable*	Response	On treatment
5. A.W	Liver	380	200	No response	On treatment†
6. P.H	Uterus	1300	280	Improvement	Complete response‡
7. F.D	Pelvis, lungs	17	10	No response	Complete response‡
8. E.K	Pelvis, lungs	800	33	Response	Complete response‡
9. H.G	Pelvis	600	4	Response	On treatment
10. P.V	Lungs, breast and pelvis	25	Undetectable*	Response	Complete response‡
11. P.R	Pelvis, lungs	11	Undetectable*	Improvement	Complete response‡
12. M.K	Unknown	55	18	Improvement	Complete response‡
13. K.B	Lungs	36	6	Improvement	On treatment
14. J.S	Pelvis	9	2	Improvement	On treatment
15. A.C	Pelvis, lungs	180	580	Progressive disease	On treatment
16. F.G	Lungs	14	13	No response	On treatment
17. G.P	Pelvis, lungs	143,000	2600	Response	On treatment
18. S.P	Lungs	20	28	Progressive disease	On treatment
19. T.K	Pelvis	7	12	Progressive disease	On treatment
20. R.M	Lungs, liver and pelvis	6	6	No response	On treatment
21. U.T	Lungs	9	5	No response	On treatment
VP16-213 alone (no prior chemotherapy)					
22. E.D	Pelvis	600	25	Response	On treatment
23. M.B	Lung	1400	110	Response	On treatment
24. P.E	Pelvis	54,000	5000	Response	On treatment
25. M.H	Lungs	26,000	3000	Improvement	On treatment
26. P.D	Pelvis	24,000	14,920	No response	On treatment

*Limit of sensitivity of HCGβ assay 2 mi.u./ml.
†Patient developed acute myeloid leukaemia while in complete remission from her choriocarcinoma.
‡Off all treatment (range 2–22 months).

Table 2. Results with VP16-213 alone and in combination in choriocarcinoma (31 patients)

	Progressive disease	No response	Improvement	>Log fall HCG
VP16-213	4	6	7	9
Vincristine + methotrexate + VP16-213	1		2	1
Bleomycin infusion + VP16-213	0		0	1
Totals	5	6	9	11

Table 3. Haematological toxicity of VP16-213

	Haemoglobin (Mean ± S.D.)	White blood count (Mean ± S.D.)	Platelets (Mean ± S.D.)
Pre-treatment	11.2 ± 1.3 (9.1–13.2)*	4722 ± 2445 (1100–9300)	260,161 ± 136,528 (68,000–614,000)
Post-treatment	10.4 ± 2.2 (8.2–12.7)	2280 ± 1710 (500–5300)	215,931 ± 153,031 (10,000–630,000)

*Figures in parentheses = range.

schedule, has minimal effect on the buccal mucosa and lining of the gut.

DISCUSSION

These results with VP16-213 in drug-resistant gestational choriocarcinoma, and the preliminary results in patients who had not received prior chemotherapy, shows that this drug has definitive activity against this tumour. VP16-213 is well tolerated with less subjective toxicity than either cyclophosphamide or actinomycin D. The role of this drug in gestational choriocarcinoma requires further assessment both in drug-resistant patients and also a first-line agent in new patients presenting with adverse prognostic factors [13]. The initial results in patients without prior treatment have produced three responses and one improvement out of 5 patients in this group. In all 5 patients the hCG has in fact fallen satisfactorily before the second course of treatment with methotrexate was started (although falling in patient 26, the hCG had not fallen far enough to be classified as an improvement by the time the second course of chemotherapy was started. See Table 1).

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