Cancer Chemother Pharmacol (1982) 7:211–214

Cancer Chemotherapy and Pharmacology

The Role of VP16-213 (Etoposide; NSC-141540) in Gestational Choriocarcinoma

Edward S. Newlands and Kenneth D. Bagshawe

Department of Medical Oncology, Charing Cross Hospital, Fulham Palace Road, London, W6 8RF, Great Britain

Summary. *Since 1976 we have used VP16-213 (Etoposide; NSC-141540) in several groups of patients with gestational choriocarcinoma. Initially we used VP16-213 in a dose of 100 mg/m² by short i.v. infusion for 5 consecutive days in patients with drug-resistant gestational choriocarcinoma. Patients were monitored with twice weekly samples for serum human chorionic gonadotrophin (HCG) concentration and a partial response (PR) has been defined as a fall in the HCG concentration to less than one tenth and an improvement (IMP) as a fall in the HCG concentration to less than one half of the pre-treatment value. In gestational choriocarcinoma patients resistant to other drugs there were 7 (19%) PR, 14 (38%) IMP, and 16 (43%) of non-responders.*

Since 1979 we have used VP16-213 as the initial agent in patients in the medium risk category [1] and up to the 1st July 1981 we have treated 38 patients with VP16-213 in this group. There have been 13 (34%) PR and 17 (45%) IMP. There are currently 30 (79%) patients in complete remission. Six are still on treatment; only two required a change of treatment because of drug resistance and so far there has been only one relapse off treatment.

We have also integrated VP16-213 in combination with methotrexate and actinomycin-D followed by vincristine and cyclophosphamide in the high risk category [1] and have so far treated 24 patients. There are 16 (67%) CR, four patients are still on treatment; only one patient failed to respond at all to therapy and there has been one relapse off treatment. There were three deaths in this high risk group. We think that VP16-213 should be regarded as one of the first line agents in treating patients with gestational choriocarcinoma who fall into the medium and high-risk categories.

Send offprint reguests to The Department of Medical Oncology Charing Cross Hospital, Fulham Palace Road, London, W6 8RF, Great Britain

Introduction

Before the introduction of systemic chemotherapy the prognosis of patients with gestational trophoblastic tumours was poor. In a review of the world literature up to 1971 Ober et al. [7] collected 84 (19%) out of 436 patients with histologically diagnosed choriocarcinoma who survived after treatment with surgery alone. Although the introduction of methotrexate in 1956 by Li et al. [5] produced a rapid improvement in the prognosis of patients with these tumours, various risk factors have been subsequently identified which affect the tendency of the tumour to become resistant to cytotoxic chemotherapy [1, 3, 4]. Bagshawe [2] analysed the causes of death in 64 patients treated at Charing Cross Hospital and of these 45 (70%) were due to drug resistance. Since 1974 patients have been ranked into low, medium and high-risk groups according to a scoring system of prognostic factors (Table 9 in 1).

Although initially gestational trophoblastic tumours are very sensitive to a number of cytotoxic agents, including methotrexate, actinomycin-D, vincristine, cyclophosphamide, and cis-Platinum in combination, once drug resistance develops further response to other cytotoxic agents has rarely produced evidence of anti-tumour effect.

We have previously reported our initial experience with VP16-213 in drug resistant gestational choriocarcinoma [6]. Since VP16-213 was so clearly an active agent we have integrated it into the initial treatment in patients who fall into the medium and high-risk categories of gestational trophoblastic tumour.

Patients and Methods

Patient Eligibility. All patients entered in these studies had gestational trophoblastic tumours which were either resistant to

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Table 1. Sequential chemotherapy for medium risk patients

a)	VP16-213 (Etoposide)	100 mg/m^2 in 200 ml of saline i.v. for 5 consecutive days
b)	MTX/FA (Hydroxyurea and 6-MP)	
	Day 1	Hydroxyurea (HU) 500 mg p.o. 12 hourly for two doses
	Day 2	MTX 50 mg i.m. at noon
	Day 3	FA 6 mg i.m. at 6.00 p.m. 6-MP 75 mg p.o.
	Day 4	MTX 50 mg i.m. at noon
	Day 5	FA 6 mg at 6.00 p.m. 6-MP 75 mg p.o.
	Day 6	MTX 50 mg i.m. at noon
	Day 7	FA 6 mg i.m. at 6.00 p.m. 6-MP 75 mg p.o.
	Day 8	MTX 50 mg i.m. at noon
	Day 9	FA 6 mg i.m. at 6.00 p.m. 6-MP 75 mg p.o.
c)	Actinomycin D	This is given on days 1–5 in a dose of 0.5 mg (total dose) i.v. for 5 consecutive days

The courses of therapy are alternated according to the following sequence: – a b c b a b c. If resistance occurs, then the ineffective regimen is replaced by Vincristine and Cyclophosphamide

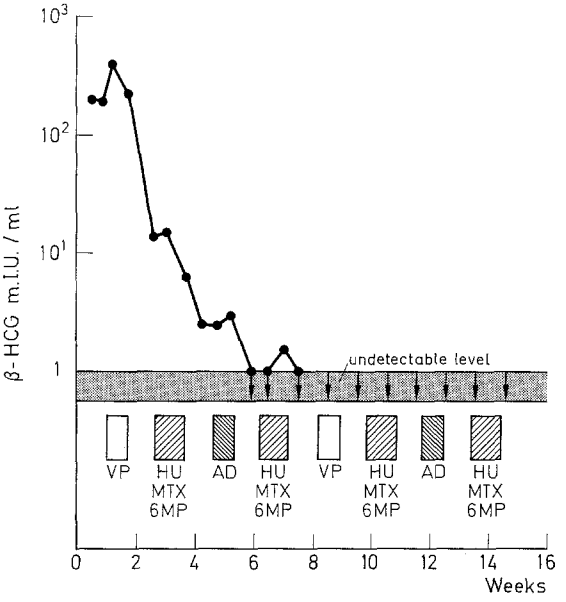

Fig. 1. HCG response in a patient wih a medium-risk choriocarcinoma. The chemotherapy abbreviations are as follows: VP, VP16-213 (etoposide); HU, hydroxyurea; MTX, methotrexate; 6MP, 6-mercaptopurine; AD, actinomycin-D

previous chemotherapy or had adverse prognostic factors at presentation [1].

Treatment Protocol. Two groups of patients were given VP16-213 in a dose of 100 mg/m^2 intravenously on 5 consecutive days. The first consisted of patients with tumours which had already become resistant to other drugs in combination and the second group were new patients with prognostic factors which placed them in the *medium-risk category* [1]. In this group of medium-risk patients VP16-213 was followed by methotrexate in combination and then actinomycin-D as shown in Table 1. The sequence of the courses of chemotherapy is shown in Fig. 1.

In the *high risk group* of patients VP16-213 has been used in combination in the following schedule (MECA):

Course 1: Day 1: VP16-213 100 mg/m^2 i.v. infusion over 30 min; Actinomycin-D 0.5 mg i.v. stat; Methotrexate 100 mg/m^2 i.v. stat; Methotrexate 200 mg/m^2 i.v. 12 h infusion. Day 2: Actinomycin-D 0.5 mg i.v. stat; VP16-213 100 mg/m^2 i.v. infusion over 30 min; Folinic acid 15 mg p.o./i.m. b.d. for four doses, starting 24 h after the start of Methotrexate.

Course 2: Day 1: Vincristine 1.0 mg/m^2 i.v. stat; Cyclophosphamide 600 mg/m^2 i.v.

Courses 1 and 2 were alternated with intervals of 6 days provided the total white blood count did not fall below 1,000 or the platelets below 50,000 or the patient developed mucositis. If severe myelosuppression or mucositis developed the next course was delayed until this had recovered.

Patient Monitoring. Patients were monitored twice weekly by radioimmunoassay specific for human chorionic gonadothrophin (HCG). This assay uses an antiserum directed at the β-subunit of HCG detects 2 IU/l (approximately equal to 0.5 nanogram per ml of HCG in the serum).

Definition of Response. Definition of response used in choriocarcinoma differs from conventional solid tumour criteria since there is a more accurate biochemical monitor of the disease in the HCG concentration. Extensive experience with this biochemical test confirms that it correlates very accurately with the behaviour of the tumour. Responses in these patients were defined as follows: a *partial response* (PR) is a fall in the serum HCG concentration to less than one tenth of the pre-treatment value (> 1-log) following a single course of therapy with VP16-213 up to the time of starting the next course of chemotherapy. An *improvement* (IMP) is a fall in the HCG to less than one half of the pre-treatment concentration following a single course of therapy up to the time of starting the next course of chemotherapy. *No response* (NR) – the fall in the HCG concentration is less than 2-fold. *Progressive disease* (PD) – a rising HCG concentration following a course of chemotherapy.

Results

There were 37 patients with drug-resistant choriocarcinoma who had been evaluated for a response to single agent VP16-213 therapy. There were 7 (19%) PR; 14 (38%) IMP, and 16 (43%) non-responders. Some of these patients subsequently went into complete remission using VP16-213 in combination but despite improvements in therapy some of these

Table 2. Results of chemotherapy in medium-risk patients with choriocarcinoma 1974–1981 (1. 7. 81)

	Chemotherapy starting with methotrexate in combination 1974–1979 Number (%)	Chemotherapy starting with VP 16-213 1979–1981 Number (%)
Complete remission	23 (60)	30 (79)[a]
Responding patients on treatment	0 (0)	6 (16)
Drug resistance requiring a change in treatment	10 (26)	2 (5)
Relapse off treatment	5 (13)	1 (2)
Death	2 (5)	0 (0)
Total	38	38

[a] Off treatment (range 0–24 months)

Table 3. Results with MECA schedule chemotherapy in high-risk Choriocarcinoma (1. 7. 81)

	Number	(%)	
Complete remission	16	(67)[a]	
Responding patients on treatment	4	(17)	
No response	1	(4)	
Relapse off treatment	1	(4)	
Death	3	(12)	(1 early death, 1 from empyema, 1 from chorio)
Total	24		

[a] Off treatment (range 0–14 months)

patients have since succumbed to their tumours with completely drug resistant disease.

Patients in the medium-risk category have been treated with sequential chemotherapy as shown in Table 1. At the start of treatment patients have received VP16-213 as a single agent, which has allowed assessment of the initial response by change in the HCG concentration. Of the 38 patients treated up to the 1st July 1981 there were four patients who could not be assessed for response to VP16-213 since their serum HCG concentration was falling after previous surgery. Four patients showed some fall in their HCG concentration which did not fulfill the criteria of PR or IMP. There were 13 (34%) PR and 17 (45%) IMP. This treatment has been well tolerated and no unexpected side effects have been observed. The majority of patients suffered complete or partial alopecia which has always been reversible on stopping chemotherapy.

Since 1974 we have been treating patients according to the prognostic score described in [1]. Table 2 shows the comparison between the group of medium-risk patients who were treated between 1974 and 1979 with methotrexate in combination as the initial agent. In this earlier group of patients the only other change in therapy was that Vincristine and Cyclophosphamide was used instead of VP16-213.

Although the numbers are fairly small our experience has been that the introduction of VP16-213 in this group of patients has improved the ease of obtaining a complete remission and reduced the chances of developing drug-resistant disease.

We have also treated 24 patients falling into the high risk category [1] using VP16-213 in combination with methotrexate and actinomycin-D. These courses have been alternated with vincristine and cyclophosphamide (MECA schedule). The concept behind this particular approach has been to try to avoid the development of tumour drug-resistance by keeping the intervals between courses of chemotherapy very short (6 days). The dosage of the drugs have also been adjusted to try to avoid cumulative toxicity. This chemotherapy has been well tolerated and despite the short intervals between treatments this schedule has been repeated for periods of 2–3 months without major cumulative myelosuppression. Analysis of the results to the 1st July 1981 are shown in Table 3. At present with the relatively short follow-up the complete resmission rate is satisfactory but the major difference from our previous intensive chemotherapy [2] in the high-risk group of patients has been the reduction of toxicity. So far there have been three deaths in this group (see Table 3).

Discussion

In total we have now treated over 100 patients with gestational trophoblastic tumours with VP16-213. VP16-213 is an active agent even in many heavily pre-treated patients with drug-resistant disease. The impressive response rate in the medium-risk category of previously untreated patients indicates that VP16-213 is one of the most active agents for this tumour. Using VP16-213 as the initial drug in the medium risk category of patient has probably improved the complete remission rate and on current analysis may have reduced the incidence of late relapse and drug-resistant disease.

So far the complete remission rate in the high-risk group is satisfactory but it will require a longer period of follow-up to know whether or not this schedule will

in fact be superior to our previous intensive chemotherapy [2]. The most impressive thing at this stage about this schedule modification has been the limited toxicity that the patients have experienced. This experimental schedule that we have used in the high-risk group of patient may be a concept that is relevant to other tumours. The biochemical monitoring of gestational choriocarcinoma by HCG indicates that rapid tumour recovery following a course of chemotherapy is a feature in patients with drug-resistant disease. In such patients it is often the slow recovery from myelosuppression which delays further cytotoxic chemotherapy for long enough for the tumour to regrow to its original or greater size. By reducing the interval between courses of cytotoxic chemotherapy to 6 days there has been surprisingly little toxicity but the dosage of drugs has to be adjusted to avoid mucositis.

Acknowledgements. We would like to thank all the gynaecologists who referred patients to us, and the staff at the Charing Cross Hospital for excellent support. We also thank Sandoz & Company Basel, Switzerland, for the initial supply of VP16-213, and Bristol-Myers Company Ltd. for continuing to supply us with this drug. We thank the Medical Research Council for support of studies on tumour markers.

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Accepted July, 1981