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Review

VM26: Phase I and II Studies

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Summary. *A review is presented of the dosage, toxicity and antitumour activity of the epipodophyllotoxin VM26, drawn from twentyfive phase I and II studies.*

Introduction

VM26 [4 demethyl epipodophyllotoxin-9-(4,6,-0-2 thenylidene β-D-glucopyranoside), or Teniposide] has been under clinical study for more than 10 years, and there are now 25 reports of phase I and II studies including 1,069 patients. In this review, the intention is to update previous reviews [8, 11, 17, 20, 24] and present the 1981 view of its spectrum of activity, dosage and toxicity and to outline the areas where its clinical activity is still to be properly assessed.

Despite being available earlier, VM26 is somewhat of a poor relation to its congener VP16-213 in the extent to which its pharmacology and clinical use have been studied, possibly because the early animal studies indicated VP16-213 to be more effective in L1210 leukaemia.

Dosage and Administration

The initial phase I study by Muggia in 1972 [16], using a weekly dose schedule in patients with normal renal and hepatic function, and normal blood count, suggested a safe starting dose was 67 mg/m^2/week, which could, subsequently, be escalated to 90 mg/m^2 in the absence of leucopenia. Since then two schedules have evolved, and are those most commonly used. They are: (a) Weekly administration at 70–100 mg/m^2 with escalation to 130 or even 180 mg/m^2 if tolerated, and with appropriate reductions in the event of leucopenia or thrombocytopenia, (b) Administration on 5 consecutive days with the course repeated at 2–4 weeks, at 30 or 60 mg/m^2/day sometimes escalating to 100 mg/m^2/day. A continuous 5-day infusion at 40–80 mg/m^2/day has been tried but seems to confer no advantage over daily administration [4].

There have been no controlled studies directly comparing toxicity or efficacy of these schedules, despite early work with L1210 leukaemia suggesting schedule dependency of the anti-tumour effect of VM26 [32].

VM26 is almost always administered by IV infusion over at least 20–30 min, more rapid infusion being associated with episodes of hypotension and cardiovascular collapse. It has also been given by intravesical installation (50 mg dissolved in 30 ml of sterile water or saline, daily for 5 days) with no systemic toxicity, but some chemical cystitis [18]. There are no reports of intracavitary use, perhaps because of animal studies [29] showing that intrapleural or intraperitoneal injection could cause chronic peritonitis or pleurisy with consequent wasting and death. Unlike VP16-213 there have been no reports of oral formulation or administration of VM26.

Toxicity

The overall impression is that VM26 is well tolerated in most schedules, and there is no doubt that the major and dose-limiting toxicity is bone marrow suppression. Any attempt to give a quantitative assessment of this toxicity by amalgamating the data from the 25 studies so far published is difficult. Most of the patients have been previously treated with radiotherapy and/or chemotherapy, but the extent of this treatment and the drugs used, which will, of course, differ in their marrow toxicity, are rarely recorded. The patients will also vary in the degree of

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Table 1. Less common toxicities of VM26 recorded in 1069 treated patients

Toxicity	No. of patients	References
Raised serum SGOT	11	[1, 3, 16, 26, 27]
Acute hypotension	10	[1, 12, 14, 16, 23, 26]
Fever	6	[3, 5, 21]
Anaphylaxis	5	[3, 7, 28]
Congestive cardiac failure	2[a]	[35]
Seizures	1[a]	[3]
Raised serum amylase	1[a]	[3]
Hypercalcemia	1[a]	[3]
Pulmonary hyaline membrane disease	1	[6]

[a] Doubtful relationship to VM26 administration

marrow involvement, this being universal in leukaemias, common in patients with lymphoma, and absent in those with brain tumours. As outlined above, the drug schedules vary, as do the modifications for toxicity and the extent of dose escalation. Last but not least the criteria for assessment of marrow toxicity are by no means standard.

In the sixteen papers in which some quantitative assessment of bone marrow toxicity is recorded, there are no less than 10 ways in which 'leucopenia' is defined or graded, and only three papers use the five grade system (0–4) as recommended by WHO [15, 34]. Not only are the definitions of leucopenia different but eleven papers record the number or percentage of *patients* with leucopenia, four papers the number or percentage of *courses* of treatment in which leucopenia occurred, and one paper the "number of cases" of leucopenia, which could mean either. Definition of thrombocytopenia is more consistent, 16 papers accepting 100×10^9/l as the lower limit of normal, one paper 75×10^9/l and one 150×10^9/l.

The actual reported percentages of leucopenia in the studies that are fairly comparable are 15–90% of patients on the weekly regime, and 28–38% of patients on the 5-day regime. Thrombocytopenia seems to be less frequent being reported in 7–30% of patients. As would be expected, more bone marrow toxicity is found in those patients with lymphoma and leukaemia, in those who have had previous chemotherapy (especially with the nitrosoureas) and at higher doses of VM26.

Nadir blood counts occur between the third and twenty first day, usually around the tenth day. Although recovery of marrow function is usually good and fairly rapid, within 7–10 days from nadir, there have been a number of deaths reported associated with profound neutropenia [7, 9, 12, 13, 14, 25].

Nausea and vomiting is not a major problem with VM26 compared to other cytotoxic agents, being reported as "mild" and "acceptable" with reported incidence of 5–19%. Diarrhoea occurs occasionally, and alopecia seems to be less common than with VP16-213 occuring in 3–9% of patients.

The other side effects reported are listed in Table 1. Acute hypotension seems as with VP16-213 to be associated with more rapid infusions, and can also occur even when the drug has been previously well tolerated [14]. It is however quite uncommon.

Antitumour Activity

If one considers only those studies in which criteria for response are clearly stated, and in which at least twelve patients are evaluable for response assessment, there are now 18 tumour types in which VM26 has been adequately assessed for anti-tumour activity (Tables 2 and 4).

It was discovered early on that VM26 had significant activity in Hodgkin's disease and non-Hodgkin's lymphoma. With the reservation that there may be double reporting of some patients, 50 patients with Hodgkin's disease are evaluable for response with a complete plus partial response rate of 40% (6% complete responders), which is an encouraging figure for single agent treatment in pre-treated patients. A similar response rate (36%) has been found in non-Hodgkin's lymphoma (Table 3). Different histological classifications have been used in the studies but if "reticulosarcoma" and "diffuse histiocytic lymphoma" are regarded as equivalent, the response rate for that subgroup is again 36% [5, 9, 14].

A response rate of 34% in pre-treated children with neuroblastoma is also encouraging [3, 22].

Assessment of response in intracerebral tumours is difficult and, in both the papers reporting treatment of primary brain tumours in adults [13, 26], "response" was defined by improvement in neurological signs or function, and in only three of the eight "responders" was the response confirmed by any improvement in either CT or isotope brain scan. These results, together with the dismal results of VM26 in primary intra-cerebral tumours in children [3, 30], even using similar response criteria, do not justify the present enthusiasm for using VM26 as a post-surgical adjuvant, or in phase III studies in these tumours.

Small cell carcinoma of the bronchus is a tumour in which, by analogy with VP16-213, one might expect VM26 to have good activity. There are two

Table 2. Tumours responsive to VM26

Tumour	References	Patients		CR	PR	CR + PR (%)
		Total	Evaluable			
Hodgkin's	[9, 14, 27]	50	50	3	17	40
Non-Hodgkin's lymphoma	[5, 9, 14]	112	111	2	38	36
Neuroblastoma	[3, 22]	52	38	1	12	34
Primary brain tumours (adults)	[13, 26]	32	32	–	8[a]	25[a]
Small cell carcinoma of bronchus	[25, 33]	39	36	2	5	19
Bladder (European)	[9, 18, 19]	65	65	4	8	18
Breast	[9, 28]	45	42	0	7	17
Acute lymphoblastic leukaemia (children)	[3, 23]	43	27	1	3	15
Colo-rectal	[28]	20	17	0	2	12

[a] Special response criteria

Table 3. Non-Hodgkin's lymphoma-response to VM26

Authors	Dose	Histology	Patients		CR	PR	CR + PR (%)
			Total	Evaluable			
EORTC 1972 [9]	30 mg/m^2/day × 5, q 10–15d	Reticulosarcoma	25	25	0	13	50
		Lymphosarcoma	19	19	0	6	32
Mathé et al. 1974 [14]	30 mg/m^2/day or 50–100 mg/m^2 weekly	Reticulosarcoma	22	22	0	8	36
		Lymphosarcoma	11	10	0	7	70
Chiuten et al. 1979 [5]	100 mg/m^2 weekly	Diffuse histiocytic	12	12	2	2	33
		Other lymphomas	13	13	0	2	15
		Total reticulosarcoma and diffuse histiocytic	69	69	2	23	36
		Total others	43	42	0	15	36
		Overall total	112	111	2	38	36

Table 4. Tumours not responsive to VM26

Tumour	References	Patients		CR	PR	CR + PR (%)
		Total	Evaluable			
Acute non-lymphoblastic leukemia (children)	[3]	28	19	1	0	5
Bladder (bilharzia-induced)	[10]	24	24	0	1	4
Non-small cell carcinoma of bronchus	[2, 25]	59	56	0	1	2
Ovary	[25]	16	16	0	0	0
Kidney	[12]	13	12	0	0	0
Oesophagus	[9]	12	12	0	0	0
Head and neck	[9]	16	16	0	0	0
Malignant melanoma	[1]	22	21	0	0	0
Sarcoma (miscellaneous)	[31]	12	12	0	0	0
Primary brain tumours (children)	[3, 30]	34	25	0	0	0

adequate studies, one of which [25] found 0/14 responses using a five drug regime at 30 mg/m^2. Woods et al. [33] using a higher dose (60–100 mg/m^2) reported 7/25 responders (28%) with two complete responses. This suggests that, in this tumour anyway, that there may be a dose-response relationship. Further studies are needed.

Bladder carcinoma, in Europe, is moderately sensitive to chemotherapy, and in a comparative study [19] a response rate of 27% was found compared to 33% for Bleomycin and 11% for Adriamycin. Response of local bladder tumours to intravesical installation of VM26 has also been reported [18]. There were two complete and one partial response out of six patients treated in this way. It is interesting that the bilharzia-induced bladder carcinoma in Egypt seems not to be responsive [10].

VM26 also has some activity against breast [9, 28] and colo-rectal carcinoma [28] and acute lymphoblastic leukaemia in children [3, 21, 23], the rather low response rate in the latter being probably explained by the extent of pretreatment and problems with haematological toxicity.

Table 4 shows the tumours in which adequate studies have shown VM26 to have little or no clinical activity.

Among the tumours in which VM26 remains to assessed adequately are acute lymphoblastic and non-lymphoblastic leukaemias in adults, testicular tumours, and solid tumours in children other than neuroblastoma.

Conclusion

What is most surprising in reviewing these phase I and II studies is the paucity of the data, considering that VM26 has been available for almost 10 years. For half the tumour types in which some adequate information is available, it comes from one paper only, and the numbers of patients are often quite small. The discrepancy in the response rates of small cell carcinoma (0 and 28%) between 2 studies illustrate the need for further studies both in this tumour and in others where data is limited, and also suggests that higher dose rates should perhaps be tried. There have been no studies directly comparing the two commonly used schedules, and only on with any data on cross resistance with VP16-213 [21].

VM26 is, however, a drug that is fairly well tolerated apart from its haematological toxicity. It undoubtedly has a role in the management of Hodgkin's disease, non-Hodgkin lymphoma, neuroblastoma and childhood acute lymphoblastic leukaemia. The evidence for its efficacy in primary brain tumours is doubtful and in small cell carcinoma of the bronchus controversial. Most importantly, however, we have no idea as to whether it is in any way a useful alternative drug to its congener VP16-213.

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