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Teniposide (VM26): an Effective Treatment for Brain Metastases of Small Cell Carcinoma of the Lung

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Abstract—*Despite good results of chemotherapy in small cell lung cancer (SCLC), occurrence of brain metastases is frequent and unaffected by commonly employed antineoplastic drugs, mainly because they do not cross the blood–brain barrier. We treated eight patients with SCLC and cerebral metastases with VM26 at* 120 mg/m^2 *given on days* 1, 3 *and* 5 *and repeated every* 3 *weeks. Two patients achieved complete response and one had partial response. Mean response duration was* 8.2 *months and survival was more than* 9 *months in responding patients. Toxicity was manageable. VM26 is an active drug in SCLC with brain metastases.*

INTRODUCTION

FREQUENT occurrence of brain metastases in small cell lung cancer (SCLC), despite the good results achieved by chemotherapy in extra-cranial sites, is thought to be due to the inability of most antineoplastic drugs to cross the blood–brain barrier [1].

Recently, it has been demonstrated that high doses of VP16 induce responses in brain metastases from SCLC, and detectable levels of the drug were found in the cerebrospinal fluid [2–4]. In this study we treated patients with SCLC and brain metastases with VM26, a congener of VP16, as a single drug at moderately high doses.

PATIENTS AND METHODS

From September 1985 to October 1986, eight patients with histologically or cytologically confirmed SCLC and brain metastases proven by CT scan were treated with VM26 at 120 mg/m^2 on days 1, 3 and 5, every 3 weeks. VM26 was diluted in 500 ml saline and infused over about 1 h. Cycles were repeated on day 22 if leukocytes were $\geq$3000/mm^3 and platelets $\geq$100,000/mm^3; otherwise therapy was delayed 1 week or until these values were reached. VM26 dose was adjusted according to nadirs of leukocytes and platelets. Corticosteroids were allowed at the start of VM26 and during the course of chemotherapy and were then tapered off gradually, when possible. Blood cell counts, 12 channel profile and chest X-ray were checked before study entry and before every cycle, thereafter. Blood cell counts were repeated weekly during the first two cycles of therapy. Brain CT scan with contrast enhancement was repeated every two or three cycles of treatment. Other diagnostic investigations were used for thorough staging of the disease and were repeated after two cycles of VM26 and as frequently as indicated thereafter, in order to assess the total response. Response in the brain was defined according to WHO criteria [5]; in addition, peripheral edema reduction was not regarded as a sign of response and patients had to have improved neurologic symptoms, without requirement of antiedemigen agents (corticosteroids or mannitol) in order to be defined as responders. At least two separate brain CT scans had to be available for adequate response assessment. Response in extracerebral sites of disease was assessed as usual [5]. Responding patients were given VM26 until progression or to patient's tolerance.

RESULTS

Overall 38 cycles of VM26 were given (2–10 per patient; mean 4.7). Treatment was given mainly on an out-patient setting. The major toxicity was myelosuppression; six patients experienced leukopenia <2000/mm^3 and one patient had severe thrombocytopenia (<50,000/mm^3). Alopecia was

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Table 1. Patient characteristics and treatment outcome

Patient	Age	Sex	P.S.	Weight loss (%)	Other metastases	Response to prior chemotherapy	Brain irradiation*	Months from diagnosis	Months from prior chemotherapy	Response to VM26	Response duration (days)	Survival (days)
A.F.	56	M	2	5–10	No	NC	No	13	1.8	NC	49+	67
B.F.	56	M	1	0	No	ADJ	No	29	23.1	PR	350	552+
D.M.	57	M	2	0	Bone	NC	No	9	3.2	NC	60+	88
E.C.	57	F	2	0	No	PR	Yes	21	17.2	CR	231	296
G.G.	61	M	1	0	No	NC	Yes	12	0.9	NC	91	119
G.P.	63	M	2	5–10	No	PR	No	12	7.5	PD	—	31
M.S.	65	M	3	>10	Lymph node	NE	Yes	6	2.1	NC	84+	84
R.R.	50	M	1	0	No	CR	Yes	14	9.5	CR	157	279

*3000 R in 10 fractions.
NC = no change; ADJ = adjuvant chemotherapy; PR = partial response; CR = complete response; PD = progressive disease.

total in all patients and emesis was mild. No heart, liver or kidney side-effects were observed.

Characteristics of patients and treatment outcome are summarized in Table 1. In six of eight patients the brain was the only site of metastatic disease at entry in the study; all had been treated by combination chemotherapy which included VP16 except one (D.M.): six had received cyclophosphamide, adriamycin and VP16 (CDE), one cisplatin and VP16 and one vincristine, cyclophosphamide and adriamycin.

All patients are evaluable for response: two achieved complete response and one had partial reduction of brain metastases after VM26 treatment. Four patients had stable disease and one progressed. The response was already present at the first brain CT evaluation (after two or three cycles). All responding patients had brain as the only site of disease at study entry; two of them had had the primary tumor radically resected and one had previously achieved a complete response to CDE and relapsed in the brain only. Moreover, responding patients had the longest time from diagnosis (mean 21 months) and the longest time from termination of prior chemotherapy (mean 16.6 months). None of them had had weight loss during 3 months before study entry and all had been treated with prior CDE chemotherapy to which two responded (the other was adjuvantly treated after initial surgery). Relapse occurred in brain again in all responding patients. One patient (B.F.) was retreated with VM26 at second brain relapse and a <50% reduction with improvement of neurologic symptoms for 5 months was seen. The mean duration of responses was 8.2 months and the three responding patients had a survival of more than 9 months from start of VM26.

DISCUSSION

Occurrence of brain metastases in SCLC is frequent and leads to death in a few months [6, 7]. Only a few anticancer drugs can actually cross the blood–brain barrier at detectable concentrations.

Postmus *et al.* have recently shown that very high doses of VP16 (1.5 g/m^2) can cross the blood–brain barrier and induce responses in patients with brain metastases from SCLC [2–4]. However, VP16 at this dose is highly toxic. VM26, a congener of VP16 has recently been shown to be one of the most active agents in SCLC [8, 9]. Despite the fact that VM26 is very lipophilic, like VP16, only minimal concentrations of the drug can be detected in cerebrospinal fluid after standard dose administration. However, a significant accumulation of VM26 had been detected in malignant gliomas and brain metastases [10].

In the present study we observed three responses in eight patients with SCLC and brain metastases. The prognostic characteristics of responding patients were better than those of non-responders and their survival was more than 9 months from start of VM26; furthermore, the treatment was well tolerated and easily handled. Our results confirm that VM26 is a highly active drug in SCLC and at the doses used responses are seen in patients with brain metastases; further testing of the drug in a larger population of patients with SCLC and cerebral metastases is warranted.

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