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Unexpected High Toxicity in a Phase II Study of Teniposide (VM-26) in Elderly Patients with Untreated Small Cell Lung Cancer (SCLC)

T. CERNY, A. PEDRAZZINI, R.A. JOSS and K.W. BRUNNER

Institut für Medizinische Onkologie der Universität Bern, Inselspital, Freiburgstraße, CH-3010 Bern, Switzerland

Abstract—*Teniposide (VM 26) as a single agent has shown promising results in the treatment of patients with small cell lung cancer. We treated 32 (30 evaluable) non-pretreated elderly and poor prognosis patients with small cell lung cancer with teniposide 100 mg/day (30 min infusion) days 1–5, every 3–4 weeks. Overall initial performance status was poor (WHO 2 or 3 in 62%). Extensive disease (ED) was documented in 50% including five patients with CNS metastases all of whom received simultaneous cranial irradiation. There was an unexpected high early death rate of 30% (9/30) including five patients with early toxic death due to severe bone marrow suppression leading to fatal septicaemia. The overall response rate was only 33% with no complete response. Where appropriate non-responding or relapsing patients received second line treatment with multidrug regimens ± radiotherapy. The overall median survival was 5.6 months [ED: 1.7, limited disease (LD): 7.5 months]. Median response duration was 5.4 months (ED: 5.1, LD: 6.7 months). For responding patients median survival was 8.8 months (ED) and 11.5 months (LD). We conclude that in elderly and poor performance status patients single agent teniposide as used in this study has an unacceptable high early death rate and that the response rate is inferior to modern standard multidrug regimens.*

INTRODUCTION

TENIPOSIDE (VM-26, 4′-demethyl-epipodophyllotoxin B-D-thenyliden glycoside) is a semisynthetic derivative of podophyllotoxin, a natural product in the root of the American mandrake (*Podophyllum peltatum*). Antitumor activity has been found in a variety of tumours including leukaemia, lymphoma, neuroblastoma and small cell lung cancer [1]. As for its congener etoposide (VP-16-213), cytotoxic effects are linked to the ability of blocking cell mitoses in late S or early G2 phases. It is also a drug known to induce pleiotropic drug resistance and to interfere with topoisomerase II [2].

Early phase II studies in previously treated patients with SCLC have shown activity at a dose level of 60 mg/m^2 i.v. for 5 days (28% OR with 2 CR; [3]) whereas no response was seen at a dose level of 30 mg/m^2 i.v. for 5 days in 11 patients [4]. Woods *et al.* also reported that increasing the dose to 100 mg/m^2 (five patients) did not improve the results; however, toxicity was markedly increased [3]. Overall these results showed a therapeutic activity of teniposide similar to VP-16 and other important active drugs such as cyclophosphamide, adriamycin and cisplatinum.

In a recent phase II study Bork *et al.* [5] have reported excellent results in previously untreated elderly patients (performance status ≤ WHO 2) with SCLC with an overall response rate of 90% including 30% CR. For a monodrug regimen these results are provocative and equal the therapeutic activity obtained by standard polychemotherapeutic regimens [6]. In the light of the low overall toxicity with no drug related death in elderly patients (median age 73) treated on an outpatient basis and a median response duration of 7.5 months these results necessitate further studies including also patients with a less favourable performance status. We therefore performed a phase II study in elderly patients including also patients with a WHO performance status grade 3.

PATIENTS AND METHODS

Thirty-two patients with cytologically or histologically proven diagnosis of SCLC were entered in a phase II study with teniposide between May 1985

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Author to whom correspondence should be addressed: T. Cerny, M.D., Institut für Medizinische Onkologie der Universität, Inselspital, Freiburgstraße, CH-3010 Bern, Switzerland.

and April 1987. None of them had been previously treated. Patients with CNS metastases at the time of diagnosis were concomitantly treated with irradiation to the brain.

All patients had bi- or unidimensional measurable disease according to WHO criteria [7]. A complete history, physical examination, biplane chest X-ray, full haematological and biochemical profile were performed. If indicated by abnormal findings additional examinations such as bone marrow examination (trephine and aspiration), liver ultrasound, CT scan of the brain, bone scintigraphy etc. were performed. Patients with impaired renal function (serum creatinine >125 mmol/l) or grossly abnormal liver tests (bilirubin >30 mmol/l) were ineligible.

Teniposide (Vumon®) at a daily dose of 100 mg (not adjusted for body surface) was dissolved in 250 ml of 5% glucose and administered as an i.v. infusion over 30 min day 1 to day 5 every 3 weeks. The treatment was postponed by 1 week if the WBC was 3.5×10^9/l or the platelet count 100×10^9/l. No antiemetics were given routinely. Therapy was given for a minimum of two cycles in all fully evaluable patients and continued until progressive disease (25% increase in size of measurable tumour) was evident. Second line treatment was given as appropriate.

Patients were considered evaluable for response if they had received at least one treatment cycle of teniposide and response was assessed according to the WHO criteria [7].

RESULTS

Of 32 patients entered into this phase II study two were ineligible: one patient showed an additional progressive metastatic malignant melanoma (despite three courses of treatment he was progressive for both diseases) and a second patient had alcoholic liver cirrhosis and impaired renal function.

The overall response rate for the 30 evaluable patients was 33% (10/30). The results are summarized in Table 2. By excluding the nine early death patients the response rate amounts to 48% (10/21). There was no complete response according to WHO criteria. One limited disease patient showed a complete disappearance of the measurable disease on chest X-ray but was still cytologically positive at bronchoscopy. This particular patient (82 years old) had a response duration of 249 days and died on day 390. He received no second line chemotherapy.

The median duration of response was 5.1 months for extensive disease and 6.7 months for limited disease patients. Median survival for all patients was 5.6 months, the respective figures for LD patients being 7.5 months (range 12–390 days, mean: 224 days) and for ED patients 1.7 months (range 4–290 days, mean 108 days) for ED.

Table 1. Patient characteristics

No. of all patients	3
No. of evaluable patients	30
Limited disease	15
Extensive disease	15
liver	8
bone marrow	1
bone	6
brain	5
other (adrenal, abd LN,* subcutaneous etc.)	11
Performance status (WHO)†	
0	3
1	7
2	13
3	7
Age (years)	
median	73
range	56–82
Male	26
Female	4

*abd LN: abdominal lymph node mass.
†See [7].

Toxicity

Of the 30 evaluable patients, eight died after the first course and one after the second course of therapy. These patients were considered 'early death' (Table 3). Of these nine patients, five died of treatment related septicaemia with WBC nadir of $0.1–0.6 \times 10^9$/l and were considered 'early toxic death'. One 62-year-old patient with liver metastases developed severe gastrointestinal pain on day 4 and was operated as an emergency. The operation showed a perforation of a gastric ulcer, he subsequently died on day 5. One patient (58 years) died at home on day 7 after a short episode of severe breathlessness and the cause of death was thought to be a central pulmonary embolism. No episode of hypotension was noted during the 5 days of treatment. He had no known history of cardiac disease but was a heavy smoker; no *post mortem* was performed. Another patient (70 years) died at home on day 6 without apparent symptoms and the cause of death remains unknown. One patient's (71 years) general well-being deteriorated rapidly after the first course and he died on day 32 without having received a second course of treatment. None of the nine early death patients received a daily dose exceding 60 mg/m^2 teniposide. Leucopenia was the dose limiting toxicity; nine patients showed leucocyte nadir values of $< 1.5 \times 10^9$/l. In 109 courses a total of 11 severe episodes of infection were observed. In 14 patients a nadir platelet count of $< 100 \times 10^9$/l was seen including four patients with $< 50 \times 10^9$/l and two patients with values $< 10 \times 10^9$/l (both of whom died because of leucopenia related septicaemia). Overall haemoglobin toxicity was mild with only one patient experiencing

Table 2. Results of treatment with teniposide in previously untreated SCLC patients

Characteristics	*n*	ED	PR*	NC	PD
Stage of disease					
Limited (LD)	15	2	6	2	5
Extensive (ED)	15	7	4	3	1
Performance status (WHO)					
G 0–1	11	0	7	2	2
G 2–3	19	9	3	3	4
Total *n* (%)	30 (100)	9 (30)	10 (33)	5 (16)	6 (20)

ED = early death, PR = partial remission, NC = no change, PD = progressive disease according to WHO [7].
*Median response duration: 5.1 months for ED and 6.7 months for LD.

grade 3 toxicity. Alopecia grade 2–3 was seen in all fully evaluable patients whereas nausea and vomiting were only mild (only two patients with WHO grade 3 vomiting). No allergic reaction or episode of hypotension was noted.

DISCUSSION

In this trial the results are disappointing with a low overall response rate (30%), no complete responders and an unexpectedly high rate of early death mainly due to septicaemia. These results were obtained despite the fact that our patients had received no prior treatment.

Our results are in contrast to the excellent results reported by Bork *et al.* with an overall response rate of 90% and a CR rate of 30% [5]. There is one major difference between the two trials: we also included seven patients with a WHO performance status of 3.

Due to our eligibility criteria we had more patients with a poor performance status, extensive disease (50% versus 36%) and also a higher number of patients with CNS disease (5 versus 1). These differences of the patient population may explain an important part of our poor results but there must be other selection biases for explaining such divergent results. They may be hidden by unknown or not reported prognostic factors. This stresses the necessity to use such prognostic factors in characterization of patients in future trials [8]. This is especially necessary in studies reporting a dramatic improvement of treatment results.

An early death rate of 30% (16% septicaemia related death) is extremely high indeed and emphasizes the importance of avoiding severe neutropenia in this group of severely ill patients. In an outpatient setting for palliative treatment of elderly patients an episode of fever may not attract the same attention as in younger patients and subsequently fatal time loss can result.

So far a single agent chemotherapy in treatment for SCLC yielding response rates and response duration comparable to the best results achieved with highly toxic polychemotherapeutic regimens has not been described except in the paper of Bork and coworkers [5]. In fact numerous studies also conducted by the same group have clearly shown that combining two or three active drugs dramatically enhances the response (overall response, complete response and response duration) in SCLC patients [9, 10]. We feel that single agent chemotherapy of SCLC remains experimental and further studies are warranted. Teniposide is certainly an active drug for the treatment of SCLC, but our results do suggest that its antitumour activity may not be superior to other well established drugs. Its important and dose limiting myelosuppressive effect will limit its use in combination with other active drugs.

We conclude that single agent teniposide in elderly and poor performance status patients has an unacceptable high early death rate and that the response rate is inferior to standard multidrug regimens.

Table 3. Toxicity of teniposide in 30 patients with SCLC

	Nadir	No. of patients
Early death (total)		9
with septicaemia		5
Leucocytes × 10^9/l	<1	6
	1–1.9	8
	2–2.9	5
	>3	11
Platelets × 10^9/l	<25	3
	25–49	3
	50–74	5
	75–99	3
	>100	16

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