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Phase I/Pharmacokinetic Study of Intraperitoneal Teniposide (VM 26)

PIERRE CANAL,*§ ROLAND BUGAT,†‡ ETIENNE CHATELUT,*‡ MARIE-CLAIRE PINEL,† GEORGES HOUIN,*‡ YVES PLUSQUELLEC‡ and MICHEL CARTON†‡

*Unité de Pharmacocinétique, Département de Biologie Clinique and †Département d'Oncologie Médicale, Centre Claudius Regaud, 20–24, rue du Pont Saint-Pierre, 31052 Toulouse, France and ‡Université Paul Sabatier, 118, route de Narbonne, 31062 Toulouse, France

Abstract—*A phase I/pharmacokinetic study of the i.p. administration of teniposide (VM 26) was undertaken. Eighteen patients with various malignancies and refractory malignant ascites consented to enter this trial. The dose escalation was made according to the modified Fibonacci scheme. Twenty-four courses were evaluable for toxicity, response and pharmacokinetics. The maximum tolerated dose was reached at* 450 mg/m^2 *and the limiting toxicity was myelosuppression, principally leukopenia. Abdominal pain occurred in one half of the courses but was not limiting. No partial remission, but two 'no change' were achieved for more than 2 months. A reduction or disappearance of ascites was seen in two patients. Pharmacokinetic studies, carried out in all courses, showed that the total exposure for peritoneal cavity averaged 10-fold greater than that of plasma. Based on the outcome of this phase I study, we could recommend phase II studies at a dose of* 390 mg/m^2 *i.p. repeated every 4 weeks with a 4 h dwell-time.*

INTRODUCTION

LARGE volume intracavitary administration of chemotherapy dialysis is an attractive way to increase the dose intensity of chemotherapeutic agents, thereby resulting in potentially increased local cytotoxicity. A recent work [1] has confirmed the effectiveness of intraperitoneal therapy with several antineoplastic agents in patients with small-volume disease.

Pharmacokinetic modelling has suggested that i.p. administration of chemotherapeutic agents by peritoneal dialysis may result in a greater area under the curve of the intraperitoneal concentrations than that of plasma [2]. Several antineoplastic agents have been experimented with in phase I trials by the intraperitoneal route (i.p.): cisplatin [3], methotrexate [4], cytarabine [5], doxorubicin [6], etoposide [7], bleomycin [8], melphalan [9] and fluorouracil [10, 11].

The pharmacokinetics of teniposide (VM 26), a semi-synthetic derivative of podophyllin, showed low levels in the peritoneum after intravenous (i.v.) administration [12]. In animals, we have demonstrated the feasibility, the pharmacokinetic advantage and the efficacy of intraperitoneal (i.p.) administration of VM 26 [13]. We believed then that such an agent should be reevaluated based on considerations related to pharmacologic advantage when given i.p. The present phase I/pharmacokinetic study was undertaken to define the maximum tolerated dose of teniposide when delivered by the i.p. route in humans and to establish the pharmacological advantage of this route of administration.

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§To whom correspondence and requests for reprints should be addressed.

MATERIALS AND METHODS

Patients

Inclusion criteria. Entry criteria included a histologically proven tumor with abdominal carcinomatosis and/or malignant ascites, a life expectancy greater than 1 month, a performance status, according to WHO criteria, level 2 or better, serum creatinine level less than 130 μmol/l, bilirubin level less than 20 μmol/l, leukocyte and platelet counts greater than 3000/mm^3 and 100,000 cells/mm^3 respectively. Patients should not have received previous irradiation to the peritoneal cavity. On the day before the treatment, an abdominal scintigraphy was performed with 3 mCi of ^{99m}Technetium microaggregated albumin to assess the adequacy of

distribution of fluid throughout the peritoneal space. Written consent was obtained from the patients before the study.

Patient characteristics. Two men (one with a head and neck epithelioma and one with gastric leiomyosarcoma) and 16 women (11 with ovarian carcinoma, two with carcinoma of unknown primary, one with sigmoid carcinoma, one with breast carcinoma and one with endometrial carcinoma) ranging in age from 41 to 70 years (median 59 years) consented to enter the study. They had received and failed to respond to prior chemotherapy; eight had failed one program and 10 two programs. Their characteristics are given in Table 1.

Experimental design and treatment plan

The peritoneal cavity was drained as completely as possible via a previously placed Tenckhoff catheter. The requisite dose of VM 26, diluted in 2 l of 0.9% NaCl solution was rapidly infused into the abdominal cavity by gravity flow. The teniposide was allowed to dwell in the peritoneal cavity for 4 h. At the completion of the 4 h dwell time, the cavity was again drained as thoroughly as possible. Following a lethal hypotension observed in one patient (see toxicity), a 1000 ml i.v. infusion of macromolecules (Dextran®, Roger Bellon Laboratories) was administered over the dwell-time to further patients ($n = 7$, nine cycles).

The starting dose of teniposide was 30 mg/m^2 body surface area. The dose was increased within and between patients according to the modified Fibonacci scheme. Since the spectrum of systemic toxicity of teniposide has already been described, we decided that only two patients should be treated at each dose level prior to escalation, with the exception of the starting dose ($n = 3$). Patients were treated every 4 weeks.

The protocol called for baseline and weekly follow-up laboratory studies including complete blood counts, platelet counts, serum creatinine measurements and liver function studies.

Pharmacokinetic protocol

To measure teniposide concentrations, peritoneal fluid (obtained through the Tenckhoff catheter) was sampled 0, 15, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min after the end of the peritoneal instillation (infusion time: 10 min in all patients). Plasma samples were obtained at the same time and then at 245, 270, 300, 480, 600, 960 and 1680 min.

Peritoneal fluid and blood samples were collected in dry glass tubes and immediately centrifuged at 4°C. The supernatant was frozen and stored at −20°C until analysis.

Teniposide concentrations were determined by HPLC using VP 16 as an internal standard, as described elsewhere [14].

Data analysis

The absorption of a drug from the peritoneal cavity is mainly a passive diffusion process [1, 15], in which the area of the peritoneal membrane (A) and its permeability to the drug (P) are involved, together with the difference of drug concentrations between the peritoneal and the systemic compartments. This absorption characterized by the product PA, can be expressed in ml/min units as a

Table 1. Pretreatment clinical data of the different patients and dose levels of i.p. teniposide administration

Patient	Age	Sex	Site of primary cancer	WHO performance status	Number of courses of prior chemotherapy	Teniposide doses (mg/m^2)
1	67	F	Ovary	2	10	30
2	54	F	Sigmoid	1	12	30
3	67	F	Unknown	2	2	30–60
4	41	M	Head–neck	1	5	60
5	63	F	Ovary	1	11	100–150
6	41	F	Ovary	0	6	100–150
7	61	F	Ovary	2	7	210
8	49	F	Breast	1	23	210–270
9	62	F	Ovary	0	5	270
10	69	F	Ovary	1	9	330
11	64	F	Ovary	2	5	330
12	63	F	Ovary	0	12	390–450
13	63	F	Endometrium	0	10	390
14	54	F	Ovary	0	9	450
15	61	F	Ovary	1	5	450–450
16	70	F	Unknown	2	5	450
17	62	F	Ovary	0	8	450
18	46	M	Stomach	1	8	450

peritoneal clearance and can be calculated according to the formula:

$$PA = \frac{-\ln\frac{C(t)}{C(0)} \times V_p}{t}$$

where C is the drug concentration, t is the time and V_p is the volume of the instilled dialysate. The peritoneal data were fitted and the peritoneal half-life was estimated using the computer program G.PHARM [16] for each course of treatment. Assuming that drug exposure for the peritoneal cavity ceased after removal of VM 26 at 4 h, the peritoneal AUC was calculated using the trapezoidal rule from 0 to 4 h.

For plasma pharmacokinetics, the terminal half-life was estimated using the same computer package, only from the terminal part of the plasma concentration time curves (following drainage). The plasma AUC was determined by the trapezoidal rule from zero to 1680 min and then extrapolated to infinity.

RESULTS

1. *Toxicity*

Twenty-four courses of intraperitoneal teniposide chemotherapy were administered to 18 patients and all of them were evaluable for toxicity.

The toxicities induced by i.p. teniposide administration are outlined in Table 2. The results of 24 courses showed that the dose limiting toxicity was a systemic myelosuppression rather than local peritoneal toxicity. The dose limiting toxicity was reached with a 450 mg/m^2 teniposide dose level which was considered to be the maximum tolerated dose (MTD). At MTD, a median nadir granulocyte count of 950/mm^3 was observed (range: 600–3500). Three out of seven patients developed a grade 3 thrombocytopenia (WHO scale) (Table 3).

Two patients experienced severe hypotension and one early death occurred, related to hypovolemia (see Table 2).

Table 2. Non-hematologic side-effects of i.p. teniposide administration (WHO scale); number of cycles with WHO toxicity level 3 or more (grade)

Dose (mg/m^2)	Number of courses	Nausea vomiting	Diarrhea	Collapsus	Pain
30	3	0	0	0	0
60	2	0	0	0	0
100	2	0	0	0	0
150	2	0	0	0	0
210	2	0	0	1 (4)	0
270	2	0	0	0	0
330	2	0	0	1 (4)	1 (3)
390	2	0	0	0	0
450	7	0	1 (4)	0	1 (3)

Abdominal pain was observed in approximately one half of the courses, which remained mild to moderate (grade 1 or 2, WHO scale), except in two cases which have required analgesics. Although it began during the drug infusion and disappeared after the draining of the cavity, no patient was forced to discontinue therapy because of abdominal pain or other local toxicities. Nausea and vomiting occurred in one half of the patients but were moderated in degree in all cases. No catheter infection was noticed, but two cases of inability to drain through the Tenckhoff catheter occurred without increased toxicities for the patients.

2. *Clinical response*

Among the six patients treated by more than one cycle of i.p. VM 26 chemotherapy, no partial response, but two 'no change' were achieved for more than 2 months.

3. *Pharmacokinetics*

The pharmacokinetics of total teniposide was determined in all courses. Figure 1 illustrates the mean profile of peritoneal and plasma levels as a function of time for the maximum tolerated dose.

The different peritoneal and plasma pharmacokinetic parameters are summarized in Table 4. The peritoneal fluid concentrations declined monoexponentially with a half-life of 8.08 ± 3.05 h whereas the mean plasma half-life was 6.91 ± 2.73 h. The mean maximum peritoneal and plasma concentrations at MTD (450 mg/m^2) were respectively 284 ± 18 mg/l and 11.53 ± 3.00 mg/l. The peritoneal clearance was constant as a function of the administered dose and showed an overall mean value of 3.27 ± 1.87 ml/min. So, there is no evidence of dose-dependent pharmacokinetics over the teniposide dose range from 30 to 450 mg/m^2. The pharmacokinetic advantage of i.p. VM 26 delivery defined as the peritoneal/plasma AUC ratio was dose-independent and ranged from 2.8 to 16.6 (mean 9.62 ± 4.84). When using the peak concentration ratio, the pharmacokinetic advantage was 27.7± 11.0.

DISCUSSION

When teniposide was administered by the i.p. route, our results showed that the maximum tolerated dose was reached at 450 mg/m^2. Myelosuppression was clearly the dose limiting toxic effect. The same limiting toxicity was observed with the analog VP 16-213 when used alone by the i.p. route at a dose of 800 mg/m^2 [17] or in combination with cisplatin at a dose of 350 mg/m^2 [7].

Two patients developed severe hypotension; this impairment has not been reversible in one who had also been treated with diuretics for massive ascites. Intra-abdominal fluid accumulation could have

Table 3. Hematologic toxicity of intraperitoneal teniposide

Dose (mg/m²)	Number of courses	Nadir leukocyte count Median (cells/mm³)	Range	Nadir platelet count Median (10³ cells/mm³)	Range
30	3	4300	3100–7500	248	98–350
60	2		7600–9800		250–320
100	2		9500–11400		375–500
150	2		3200–3800		306–383
210	2		3300–3800		185–450
270	2		3000–3900		170–260
330	2		5200		260
390	2		2900–4700		220–250
450	7	950	600–3500	90	39–205

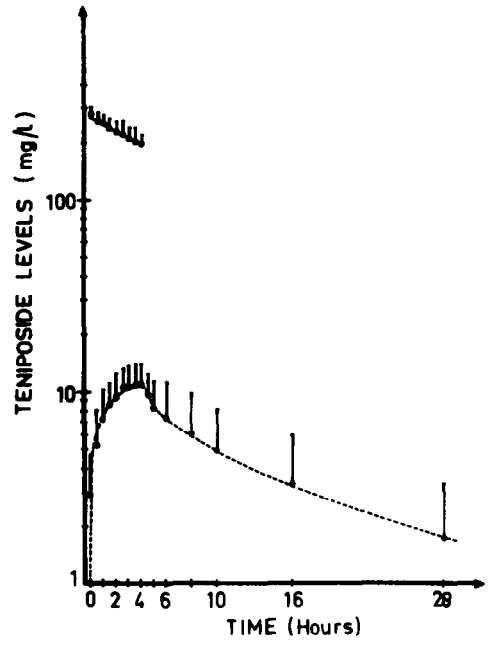

Fig. 1. Mean of measured teniposide concentrations in seven patients after i.p. administration of 450 mg/m². —o— *Peritoneal concentration;* ---•--- *plasma concentration; points: mean; bars, S.D.*

facilitated the occurrence of teniposide hypersensibility [18]. One can notice that further infusion of macromolecules over the dwell-time period encompassed that severe side-effect. However, drastic caution will have to be paid when delivering teniposide i.p. in patients with a poor hemodynamic condition due to a large volume of inflammatory peritoneal fluid.

During this escalation-dose study, VM 26 did not outline any neotoxicity related to the new route of administration investigated.

Although abdominal pain occurred, it was not dose-related and was not responsible for the dose limiting toxicity, as for Adriamycin® [6], mitomycin [19], mitoxantrone [20, 21] or aclacynomycin [22]. Therefore, the dose of teniposide could be increased until systemic toxicity became dose-limiting. Consequently, the i.p. administration of teniposide allows drug delivery to the more superficial layers of tumor nodules with very high drug concentrations through local diffusion, while drug delivery to the core of tumor nodules by capillary blood flow provides drug levels equivalent to those resulting from i.v. drug administration. This two route concept described by Howell [3] can apply to drugs which have the following two properties: a steep dose–response relationship and either a direct or a metabolic-activated cytotoxicity within tumor tissue. These two properties have been described for teniposide [24, 25].

Peritoneal maximum concentrations were at least 200-fold higher than those obtained after i.v. administration of 100 or 150 mg/m² teniposide [26]. At the MTD, the plasma exposure determined by plasma AUC (159 ± 75 mg/l × h) was equivalent to the AUC after 24 h i.v. infusion of 150 mg/m² teniposide (176 mg/l × h) and greater than that observed after 1 h i.v. infusion of 100 mg/m² (105 mg/l × h) [26].

The pharmacokinetic data showed that the decrease in peritoneal concentration is of first order and, even at very high peritoneal concentrations, the peritoneal clearance was not saturated. The pharmacological advantage of i.p. administration of teniposide in terms of the peritoneal:plasmatic AUC ratio averaged 10. This was a substantial advantage for peritoneal administration equivalent to that measured with methotrexate [4], cisplatin [3], VP 16 [7] and bleomycin [8], but lower than that found for many other anticancer drugs (aracytine [5], 5-fluorouracil [10] or thioguanine [27]). VM 26 is a highly protein-bound drug (close to 0.99) [28]. Since the peritoneal dialysate is relatively protein free as compared to the plasma, the differential exposure of free drug in the peritoneal cavity relative to the plasma should be even more important. As we have not determined free teniposide concentrations in the peritoneum and the plasma, one can only assume that point. At the end of the 4 h dwell-time, only 30% of the administered

Table 4. Pharmacokinetic parameters of teniposide after i.p. administration mean and standard deviation (in parentheses)

	Peritoneum				Plasma			Peritoneum/plasma	
Dose (mg/m²)	Peak (mg/l)	AUC* (mg/l × h)	$T_{1/2}$ (h)	*PA* (ml/min)	Peak (mg/l)	AUC† (mg/l × h)	$T_{1/2}$ (h)	Peak ratio	AUC ratio
30	18	59	10.5	2.57	0.66	4.9	7.1	28.9	12.9
	(1.6)	(10)	(4.7)	(0.89)	(0.16)	(1.1)	(1.3)	(8.6)	(3.7)
60	31.6	195	6.8	3.81	1.15	8.5	5.5	31.5	13.9
	(4.8)	(22)	(2.3)	(1.29)					
100	55.5	184	7.2	3.28	2.34	17.9	4.9	22.7	10.3
	(1.5)	(5)	(1.3)	(0.59)	(0.13)	(0.9)	(0.1)	(2.9)	(0.8)
150	78.6	261	9.4	2.47	3.09	24.9	4.1	21.2	10.5
	(1.4)	(1)	(0.9)	(0.22)	(0.22)	(1.3)	(0.4)	(4.3)	(0.6)
210	102	345	9.9	2.40	4.15	47.2	5.8	25.3	8.4
	(3.0)	(14)	(1.5)	(0.35)	(0.70)	(18.6)	(0.2)	(3.6)	(2.9)
270	166.5	507	4.4	6.74	5.37	95.5	10.6	49.3	14.0
	(45)	(81)	(0.3)	(1.91)	(2.72)	(64.2)	(1.4)	(15.1)	(0.4)
330	167.5	565	11.0	2.18	6.06	43.2	4.1	33.5	16.1
	(35.5)	(131)	(2.1)	(0.2)	—	—	—	—	—
390	235.5	756	5.7	5.04	9.03	117.1	7.5	29.5	9.5
	(14.5)	(33)	(0.1)	(0.17)	(3.32)	(68.0)	(2.5)	(9.2)	(5.2)
450	283.1	941	7.7	2.70	11.52	158.6	7.6	26.0	7.4
	(17.2)	(101)	(2.1)	(1.93)	(2.78)	(70.0)	(2.7)	(7.6)	(4.3)
Mean			8.08	3.27			6.91	27.7	9.62
S.D.			(3.06)	(1.87)			(2.73)	(11.0)	(4.84)

*AUC (0–4 h).
†AUG (0–∞).

dose was absorbed. This amount was responsible for the hematologic limiting side-effect. Consequently, one can guess that any increase of the dwell-time would reduce the DMT to such an extent that no extrapolation, regarding the recommended dose, could be drawn from our present study.

Current clinical studies [7] try to find new combinations of drugs which might have synergistic cytotoxicity with CDDP as 5-FU [29] or VP 16 [7]. On this basis, we recently initiated a phase I and pharmacokinetic study of intraperitoneal cisplatin and teniposide administration.

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