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Pharmacokinetics of VM 26 given intrapericardially or intravenously in patients with malignant pericardial effusion

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Summary. Three patients with lung cancer (1 SCLC, 2 NSCLC) and pericardial malignant effusion received 100 mg/m^2 Teniposide (VM 26) i.v. and, 1 week later, 50 mg/m^2 intrapericardially. Plasma, pericardial, and urine levels of the drug were measured in all patients after the two treatments by a HPLC assay. After intrapericardial administration, a high VM 26 concentration was found in the pericardial cavity and slow systemic drug absorption was observed. Since the drug AUC after intrapericardial administration was approximately 15–21 times that after i.v. administration, it could be that this treatment is more effective against neoplastic deposits localized in the pericardium. Even though this small series does not permit conclusions to be drawn on the efficacy of VM 26 given intrapericardially, the lack of local toxicity, minimal systemic toxicity, and the response observed in two out of three patients given intrapericardial VM 26 suggest that further investigation should be carried out on this method of VM 26 administration.

Introduction

The pericardium may be the site of metastatic disease for almost any primary malignant tumor. Although neoplastic involvement of the pericardium may be asymptomatic, the progressive accumulation of malignant pericardial effusion may result in acute life-threatening cardiac tamponade. Reportedly, pericardial involvement was the immediate cause of death in 36% of cancer patients with pericardial effusion and contributed significantly to death in a further 49% [24].

The management of malignant pericardial effusion remains controversial. A short-term palliation of the symptoms caused by this fluid can be achieved by creation of a pericardial-pleural window or pericardiectomy. The direct intracavitary instillation of sclerosing agents or radioactive compounds, as well as the use of radiotherapy, have all been reported to reduce the rate of reaccumulation of pericardial fluid in patients with malignant effusion [6, 20–22].

Recently, intracavitary administration of antineoplastic agents (intraperitoneally or intrapleurally) has been tested, and in some cases it has given promising results [2, 4, 13–18, 23]. The rationale for this method of administration is to attain higher, longer-lasting drug concentrations in the cavity where metastatic deposits or floating malignant cells are present with lower plasma doses and less systemic toxicity. No data are available on the efficacy and pharmacokinetic behavior of antineoplastic agents given intrapericardially.

In this study we compared the pharmacokinetic behavior of teniposide (VM 26), a drug reportedly active in small cell lung cancer [3], which was administered intrapericardially and i.v. to three patients with lung cancer and symptomatic pericardial effusions.

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Patients and methods

Patients. Three male patients aged between 54 and 66 years with malignant pericardial effusions entered this study. Patients 1 and 2 were suffering from NSCLC, patient 3 from SCLC. Their performance status was 40, 40, and 30: patient 1 had previously received radiotherapy; patient 2 a combination of *cis*-platinum and etoposide and, subsequently, radiotherapy; and patient 3 *cis*-platinum and etoposide. In patient 3 cardiac tamponade occurred, requiring urgent evacuation.

All three patients had normal renal (serum creatinine 0.6–1.2 mg/100 ml) and hepatic function (total bilirubin 0.15–1.0 mg/100 ml; SGOT and SGPT <20 U/ml). Patient 3 had elevated γGT and alkaline phosphatase. Cytological examinations showed tumor cells in the pericardial effusions.

Drug treatment. A polyethylene catheter was inserted in the pericardial space under local anesthesia and echocardio guidance. Patients 1 and 2 first received a dose of VM 26 (Vumon, Brystol Myers, N.Y., USA) 100 mg/m^2 as a 4-h infusion, and 8 days later they received 50 mg/m^2 VM 26 in the pericardium as a 4-h infusion. Patient 3, who had the cardiac tamponade, received VM 26 intrapericardially before the i.v. treatments.

Sample collection. At various times during and after the VM 26 infusion, 1–2 ml of pericardial fluid and 2–3 ml blood samples were collected, immediately put into heparinized tubes, and centrifuged at 3,000 rpm for 10 min. The supernatants were stored at −20° C until analysis.

Samples were taken at the following intervals: 0 (baseline); 2, 4, 4.5, 5, 6, 7, 8, 12, 28, 40, 52, and 76 h from the start of the 4-h infusion. Urines were collected 48 h after the start of infusion and were stored at −20° C until they were analyzed.

Drug assay. The method used to determine VM 26 in plasma, pericardial fluid, and urine samples has been previously described by Evans et al. [11]. Briefly, 0.5–1 ml plasma, 1 ml pericardial fluid (for intrapericardial administration, pericardial fluid was diluted 1:5), or 0.5 ml urine was extracted with 8 ml chloroform containing VP 16 (50 µl of a 100 µg/ml solution) as internal standard. After 20 min shaking at room temperature, samples were centrifuged at 3,000 rpm for 20 min at 4° C. The organic phase was dried under vacuum and then redissolved with 100 µl methanol; 10–20 µl of this solution was injected into a Waters Model 6000 A HPLC equipped with a 254 nm absorbance detector.

Separation was achieved using an isocratic solvent system of water-to-acetonitrile-to-acid acetic (64:35:1) at a flow rate of 1 ml/min, using a 25 cm long Micro-Bondapak Phenyl column purchased from Waters Assoc., New York, N. Y., USA.

For the determination of VM 26 aglycone glucuronide, urine samples were incubated with β-glucuronidase-arylsulfatase at 37° C for 24 h; to 1 ml of urine, 1 ml 0.1 *M* acetate buffer, pH 4.5, was added with 50 µl (Corresponding to 250 mU) β-glucuronidase-arylsulfatase (from Helix Pomatia Boehringer-Biochemia Robin, Italy). In parallel, identical samples were treated similarly except that no β-glucuronidase arylsulfatase was added.

All samples were then extracted and injected into an HPLC column as previously described for VM 26, but using a mobile phase of water-to-acetonitrile-to-acetic acid (74:25:1) at a flow rate of 1.2 ml/min.

Pharmacokinetic analysis. VM 26 half-life in pericardial fluid and plasma was determined by regression analysis of the concentration time data of the log linear phase. The area under the concentration (AUC) versus time curves was calculated using the trapezoidal rule from 0 to the last measured time point and extrapolated using the estimated half-life.

Results

Two out of three patients (nos. 2 and 3) had no reaccumulation of pericardial fluid for 2 and 5 months after intrapericardial VM 26; in both cases when the catheter was taken out, it was possible to drain only a few milliliters of fluid which was cytotologically negative. In patient 1, the response could not be evaluated because the pericardial effusion contained much blood. Neither local nor systemic toxicity was detected in patients 1 and 3, while patient 2 presented mild leukopenia (WHO grade 1).

After intrapericardial infusion (50 mg/m^2), VM 26 disappeared from the pericardial cavity following a biphasic pattern with $t\frac{1}{2}$ β ranging approximately from 9 to 16 h. Pericardial levels (Fig. 1) remained over 10 µg/ml for 40 h with a mean peak of 195 ± 4.5 µg/ml; the plasma concentrations were approximately 100 times lower, ranging from 0.7 to 1.7 µg/ml. Figure 2 shows the plasma and pericardial fluid levels of VM 26 in the same patients receiving 100 mg/m^2 as a 4-h intravenous infusion. After 8–12 h, the pericardial concentrations reached their maximum (4–4.8 µg/ml) and then remained higher than the corresponding plasma concentrations. VM 26 peak levels $t\frac{1}{2}$ β, and AUC values in plasma and pericardial fluid are compared in Table 1 after each route of administration.

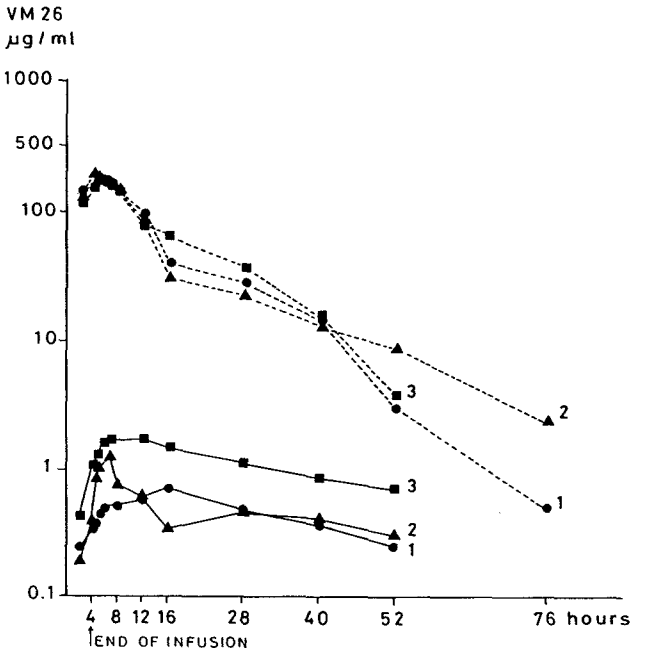

Fig. 1. Plasma (*solid lines*) and pericardial (*dotted lines*) levels of VM 26 during and after 50 mg/m^2. VM 26 was given as an intrapericardial infusion

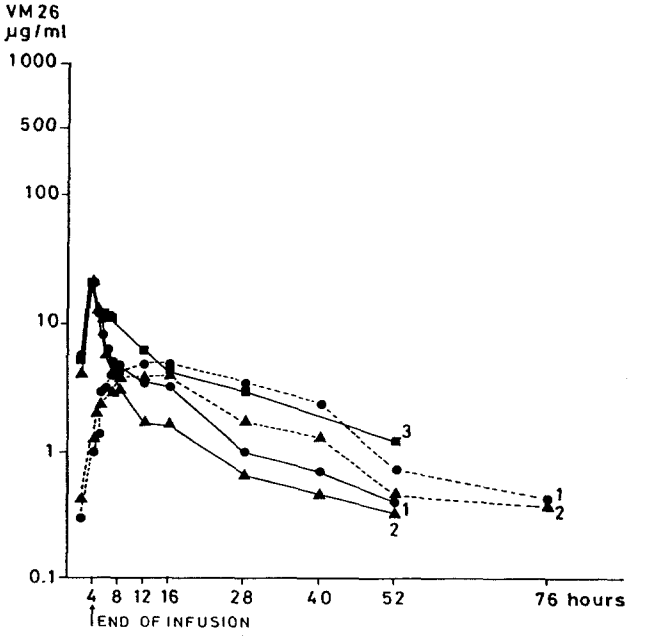

Fig. 2. Plasma (*solid lines*) and pericardial (*dotted lines*) levels of VM 26 during and after 100 mg/m^2. VM 26 was given as a 4-h i.v. infusion

As shown in Table 2, the amount of VM 26 and VM 26 aglycone glucuronide found in the urine collected for 48 h after the start of infusion ranged from 1% to 15% and from 2% to 20% of the dose; urinary elimination was greater after i.v. than after intrapericardial administration.

Table 1. Pharmacokinetic parameters of VM26 in patients receiving 100 mg/m² as a 4-h i.v. or 50 mg/m² as a 4-h pericardial (ipc) infusion

Patient no.	Route	Dose (mg/m²)	Pericardial fluid			Plasma		
			Peak (ug/ml)	$t_{1/2}\beta$ (h)	AUC (ug/ml · h)	Peak (ug/ml)	$t_{1/2}\beta$ (h)	AUC (ug/ml · h)
1	i.v.	100	4.8	15.8	177	20.6	11.9	141
2	i.v.	100	4.0	16.9	126	21.0	10.9	78
3	i.v.	100	n.c.	n.c.	n.c.	22.8	11.7	250
1	ipc	50	199	8.9	2649	0.7	25.7	32
2	ipc	50	198	16.1	2663	1.3	36.5	41
3	ipc	50	190	9.1	2848	1.7	31.5	90

n.c. = not collected

Table 2. Urinary excretion of VM26 and aglycone of VM26 after i.v. and intrapericardial (ipc) administration

Patient no.	Route	Total dose of VM26 (mg)	Urinary excretion of VM26 (% dose)	Urinary excretion of VM26 aglycone (% dose)
1	i.v.	180	10.7	2.1
2	i.v.	184	7	5.1
3	i.v.	210	15.4	20.4
1	ipc	90	1.7	3.7
2	ipc	91	1.2	2.9
3	ipc	105	n.c.	n.c.

n.c. = not collected

Discussion

The present study shows that following intrapericardial administration of VM 26, very high drug levels are achieved and maintained in the pericardium compared to those found in the pericardial fluid after i.v. administration. Pericardial AUCs after 50 mg/m² VM 26 intrapericardially were 15–20 times those after i.v. administration of 100 mg/m². The toxicity in this method of drug delivery is less than by the i.v. route, which is consistent with the data found by Allen et al. [1], i.e., that VM 26 given i.p. was essentially non-toxic compared to the i.v. route.

The tendency of VM 26 to accumulate in neoplastic effusions was already been suggested by previous studies, which showed that 24 h after i.v. infusion the drug levels are higher in ascites than in plasma. This may be related to its high molecular weight [9]. Studies in vitro have indicated that the concentrations and – even more – the exposure time are crucial for epipodophyllotoxin cytotoxicity [7, 12]. Therefore, neoplastic cells floating in the pericardium are likely to be more susceptible to the higher, longer-lasting VM 26 levels attainable by administering the drug directly into the cavity.

It is more difficult to predict whether this method of administration is advantageous in the case of a metastatic deposit. It can be predicted that the larger a metastatic deposit is, the lower the chances that VM 26 will penetrate efficiently enough to attact a large proportion of neoplastic cells [8].

Animal studies to define the intracellular drug concentration according to the size of metastatic deposits exposed locally to drugs are required to provide a rational basis for establishing the cases in which this approach is theoretically advantageous [5, 10].

As previously reported, only a small percentage of the VM 26 dose was eliminated by the renal route. VM 26 urinary excretion varied between 7% and 15% after i.v. administration. Its elimination appeared related to the plasma levels since, after intrapericardial administration, there was a lower drug plasma AUC and much less urinary excretion. We confirm our previous findings [19] that VM 26 aglycone glucuronide is a major urinary metabolite; its amount in the urine ranged between 2% and 20% of the dose. Total elimination of VM 26 and VM 26 aglycone was therefore about 12% in patients 1 and 2 and 35% in patient 3. In the latter patient, who showed the lowest VM 26 plasma clearance, it is possible that lower biliary excretion due to liver cholestasis was partially compensated for by greater drug elimination via the renal route.

In conclusion, the present study extends clinical pharmacokinetic knowledge on the anticancer agent VM 26 and provides a kinetic rationale for using this drug intrapericardially. Further studies are needed to define in which patients this route of administration is advantageous and to evaluate its efficacy in comparison to more traditional methods of drug delivery.

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