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Intrapleural etoposide for malignant effusion

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Summary. The pharmacology, toxicity, and therapeutic effectiveness of etoposide (VP-16) given by the intrapleural route were examined in a phase I trial. Ten patients with malignant pleural effusion received 100, 150, or 225 mg/m^2 VP-16 infused over 2 h into the pleural space after drainage of pleural fluid. The administration of VP-16 was tolerated well, with no local pain, increase in cough, dyspnea, or infection. Myelosuppression was mild at doses of 150 mg/m^2 or less but severe at 225 mg/m^2. Drug levels were followed in both plasma and pleural fluid for up to 12 h. Clearance of VP-16 from the pleural cavity was low at 2 ml/min m^2. Peak pleural-fluid drug levels in patients receiving 225 mg/m^2 exceeded 300 μg/ml, whereas peak drug concentrations in corresponding plasma samples obtained at the same time amounted to <10 μg/ml. Serial chest X-rays showed no disappearance of pleural effusion in nine evaluable patients. However, follow-up investigation of pleural fluid characteristics [carcinoembryonic antigen (CEA), lactic dehydrogenase (LDH), and cytologic examination] suggested some evidence of local therapeutic benefit.

Introduction

The current approach to treating malignant pleural effusion consists of palliation, except in patients whose tumors are highly sensitive to systemic therapy. Generally, repeated thoracentesis is followed by pleurodesis with various sclerosing agents and by the apposition of the pleural surfaces as the negative pressure of a chest tube is applied. More aggressive approaches include parietal pleurectomy and hemithoracic radiation therapy. These maneuvers are intended to destroy the fluid-producing capability of the parietal pleura but are not directed at the presence of cancer cells in the pleural space and draining lymphatics.

A more comprehensive approach involves instillation of a chemotherapeutic agent into the pleural cavity with the intent of killing malignant cells in the effusion and on the pleural surfaces. Drugs of this type have included 5-fluorouracil [2, 11], bleomycin [1, 8], methotrexate [5], or a combination [7]; their major side effects were local pain, transient fever, and occasional myelosuppression.

We present a phase I study of intrapleural etoposide (VP-16). This drug was chosen because of its lack of caustic properties, which enables repeated instillation, its broad spectrum of antitumor efficacy, and the demonstration of its safety in a single case report [6].

Materials and methods

Patients. All patients with a pleural effusion related to a malignant condition were considered for the study; those with effusions secondary to unrelated medical problems were excluded. The effusion had to be part of a malignant disease that was either unlikely to respond to standard or investigational systemic therapy or had recurred and was unlikely to respond to additional systemic therapy. Causes for exclusion were serum creatinine levels of >1.5 mg/dl, serum bilirubin values of >1.5 mg/dl, a white cell count of <3,500/mm^3, a platelet count of <150,000/mm^3, a performance status of >3 (Zubrod scale), an abnormal coagulation profile, and chemo- or radiotherapy during the preceding 21 days.

Thoracentesis was done first and the pleural fluid was evaluated for cytologic characteristics, pH, specific gravity, protein, cell count, lactate dehydrogenase (LDH), and carcinoembryonic antigen (CEA). These evaluations were repeated on days 8, 15, and 29.

Drug administration. A dose of 100 mg/m^2 VP-16 diluted in 500 ml normal saline was infused over 2 h into the pleural space after the effusion had been completely drained. This was repeated on days 8 and 15, and the cycle of three once-weekly intrapleural infusions was repeated every 4 weeks. A 50% dose escalation was allowed if only grade 0–1 toxicity occurred and if the lowest absolute granulocyte count was >2,000/mm^3 and the lowest platelet count, >100,000/mm^3. Of the ten patients studied (Table 1), four received the first cycle of infusions at 100 mg/m^2 per infusion, the next three began with 150 mg/m^2, and the last two with 225 mg/m^2. Patient 4 was never treated. Dose escalation was allowed for each patient in succeeding cycles.

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Table 1. Patient characteristics

Patient number	Age (years)	Gender	Histology of lesion	Primary site	Previous chemotherapy	Previous radiotherapy	Evaluability	Number of intrapleural VP-16 cycles
1	56	F	Adenocarcinoma	Right lung	No	No	Yes	11
2	70	M	Squamous-cell carcinoma	Right lobe	Lomustine	No	Only 2 of 3 intrapleural infusions because of respiratory arrest secondary to chronic lung disease	
3	62	F	Adenocarcinoma	Breast	FAC, CMF, tamoxifen megestrol acetate, vinblastine	Yes	Yes	2
4	38	F	Adenocarcinoma	Left lung	CEP × 1	No	No: pneumothorax requiring chest-tube insertion	0
5	57	F	Adenocarcinoma	Breast	CMF × 6; tamoxifen vinblastine, doxorubicin × 5	Yes	Only 2 of 3 intrapleural infusions because of Heimlich valve insertion	
6	70	M	Lymphoma,	Stomach,	CHOP-Bleo × 8, MIME × 11	No	Yes	2
			Adenocarcinoma	Lung	No	No		
7	64	F	Adenocarcinoma	Right and left breast mesothelioma	No	Bilateral chest	Yes	2
8	54	F	Adenocarcinoma	Right and left breast	Tamoxifen	Bilateral chest	Yes	2
9	69	F	Adenocarcinoma	Right lung	No	No	Yes	1
10	62	F	Adenocarcinoma	Right lung	CEP × 1	No	Yes	1

FAC: 5-fluorouracil, Adriamycin, cyclophosphamide; CMF: cyclophosphamide, methotrexate, 5-fluorouracil; CEP: cyclophosphamide, etoposide, cisplatin; CHOP-Bleo: cyclophosphamide, Adriamycine, vincristine, prednisone, bleomycin; MIME; Methyl-Gag, ifosfamide, methotrexate, etoposide

Table 2. Hematologic toxicity of intrapleural VP-16

Dose	Courses	Median (nadir × 1,000) of:	
	(*n*)	Absolute granulocyte count (day) and range	Platelet nadir (day) and range
100 mg/m²	4	3.5 (15.5) 3.2–5.2	274 (5.5) 255–309
150 mg/m²	15	1.4 (24) 0.6–4.8	227.5 (12) 117–335
225 mg/m²	5	2.9 (22) 0.6–6.0	385 (22) 149–453

Pharmacology of VP-16. We evaluated the pharmacology of intrapleural VP-16 by simultaneously obtaining samples of plasma and pleural fluid at 1, 2, 4, 8, 24, and 48 h after the end of the infusion. Drug levels were determined by high-performance liquid chromatography (HPLC) using a modification of the method developed by D'Incalci et al. [3]. Samples were extracted by adding 8 ml chloroform to 1 ml plasma or pleural fluid, followed by shaking for 10 min and centrifugation at 1,000 *g* for 15 min at 4° C. Next, 6 ml of the chloroform layer were dried under nitrogen. The residue was reconstituted in mobile phase and 40-µl aliquots were injected onto the HPLC column.

Chromatography was done on a Waters Associates (Milford, Mass) µBondapak CN HPLC column (150 × 3.9 mm). The mobile phase consisted of methanol : water (40 : 60, v/v) at a flow rate of 1 ml/min. Absorbance was measured at 254 nm. Extraction efficiencies of VP-16 from biological fluids were 78% ± 3% for plasma and 84% ± 6% for pleural fluid. The lower limit of detection of drug from either fluid was 0.5 µg/ml. Within-day assay coefficients of variation for drug extracted from plasma or pleural fluid were 4.8% and 3.7%, respectively. Between-day coefficients of variation for all drug assays were <12%.

Pharmacokinetic parameters were determined by model-independent methodology [9]. The AUC was calculated using the trapezoidal rule, extrapolating from the last sampling time, t, with the formula:

$$AUC_{\infty} = C_{pf}\,dt,$$

where C_{pf} is the concentration of drug measured in the pleural fluid. The mean residence time (MRT) can be defined as the mean time for intact drug molecules to transit through the body (or from a body cavity) and involves a composite of all kinetic processes. MRT was calculated according to the formula:

$$MRT = AUMC_{\infty}/AUC_{\infty},$$

where $AUMC_{\infty}$ is equivalent to the area under the first moment curve. It can be defined as the area under the curve of the product of t and C_{pf} from time zero to infinity.

Table 3. Pharmacologic actions of intrapleural VP-16

Patient	Dose (mg/m2)	AUC (mg h/l)		MRT (h):		Clearance from pleural fluid (ml/min m²)
		Pleural fluid	Plasma	Pleural fluid	Plasma	
E. D.	100	1,046	71	13	5	2
V. B.	100	572	88	4	8	3
C. M.	100	1,940	22	13	4	1
B. H.	100	964	61	7	7	2
T. S.	150	1,930	130	3	4	1
L. E.	150	1,289	75	8	8	2
D. J.	225	2,130	75	6	11	2
A. U.	225	2,199	115	5	9	2
Mean ± SD				7±4	7±3	2±0.6

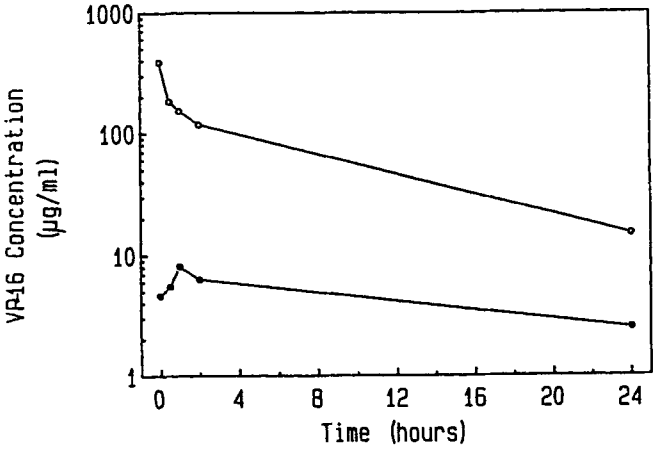

Fig. 1. Pharmacology of pleural and plasma VP-16 in patient 10. ○, pleural fluid concentration; ●, plasma concentration after 225 mg/m² intrapleural VP-16

Results

As Table 1 shows, the ten patients had been heavily treated in the past; their performance status was generally good. Patients 2 and 5 received only two VP-16 infusions during their first treatment cycle. During the course of this study, 4 patients received 5 cycles at 100 mg/m², 5 patients received 15 cycles at 150 mg/m², and 3 patients received 3 cycles at 225 mg/m². The intrapleural instillations of the drug were well tolerated, with no local pain, no increase in dyspnea or cough, and no chest wall recurrence or infection. The absence of pleural reaction enabled repeated instillation.

Mild systemic toxic effects consisted of progressive alopecia, emesis, and malaise. Myelosuppression (Table 2) did not occur at 100 mg/m² and was mild at 150 mg/m², although delayed until days 22–30. Myelosuppression was more severe at 225 mg/m², with a granulocyte nadir of 575/mm³ in one course, but no infection or thrombocytopenia was observed. The patients had no renal, hepatic, cardiac, or pulmonary toxic reactions.

Pharmacologic studies

Pharmacologic studies were done on the plasma and pleural fluid from eight patients, of whom four had received 100 mg/m² infusions and two each had received 150 and 225 mg/m² (Table 3, Fig. 1). The AUC of VP-16 in the pleural space increased with dose, but the number of patients evaluated was considered too small to demonstrate a strict dose-response relationship. This was also true for AUC determinations in plasma.

The MRT was 7 h in both the pleural space and plasma (Table 3). Drug clearance from the pleural space was low at 2 ml/min m². The average AUC ratio of VP-16 in pleural fluid to that in plasma was 31 at 100 mg/m², 16 at 150 mg/m², and 23 at 225 mg/m², which indicated a much greater exposure of pleural space to drug by intrapleural injection than could have been achieved by systemic drug administration. Interestingly, however, the plasma AUC after intrapleural administration was comparable with that previously reported for VP-16 after intravenous injection [4, 10], which suggests that once the drug is outside the pleural cavity, its rate of elimination from the body is similar to that after systemic drug administration. As Fig. 1 shows, administration of an intrapleural dose of 225 mg/m² resulted in a peak pleural fluid level of 387 µg/ml immediately after drug infusion ended. In contrast, plasma levels in the same patient peaked at 8 µg/ml at 1 h.

Therapeutic results

Serial chest X-rays showed no disappearance of the pleural effusion in the nine evaluable patients (two partially evaluable, seven fully evaluable). However, serial follow-up of the pleural fluid characteristics showed changes suggestive of local therapeutic benefit. Cytologic examination was positive for malignancy in all ten patients on initial evaluation, could be followed in seven patients, and became negative in four cases. CEA levels in pleural fluid were elevated above 1.5 ng/ml in seven patients, below 1.5 ng/ml in two, and were unknown in one; the elevated

values fell in three of seven cases. LDH levels in pleural fluid were above 225 IU/ml in three patients, below 225 IU/ml in three, and not available in four. The abnormal values fell in all three patients, in conformity with changes in cytology and CEA level, and values rose from normal in another patient while cytologic characteristics and CEA values normalized.

Discussion

Although a large body of information is now available concerning the therapeutic response and toxic effects associated with intraperitoneal chemotherapy, relatively little has been written about the therapeutic advantages or disadvantages of intrapleural administration of specific chemotherapeutic agents against malignant pleural effusions. This knowledge is so limited because of the practice of immediate pleurodesis, which makes all further intrapleural chemotherapy impossible, and also because early metastatic spread to other sites occurs frequently, particularly in patients with lung and breast cancer.

The criteria for choosing a drug for intrapleural chemotherapy should include known efficacy against the particular malignancy, lack of sclerosing properties, and low transfer to the systemic circulation. These properties would enable high local cell kill, repeated access to the pleural space, and tolerable systemic toxicity.

Our experience indicates that intrapleural VP-16 is well tolerated and that enough drug escapes into the systemic circulation to act as a "second route" of chemotherapy. Because a single agent, such as VP-16, is unlikely to produce a therapeutic benefit in heavily pretreated patients, a combination of drugs should be considered in the future. The weekly schedule was chosen in this phase I trial to enable pharmacologic evaluation. A daily schedule would be preferable in future trials. Synergism between drugs would also be a desirable feature. The evaluation of therapeutic responses appears to be difficult but not impossible; it should include follow-up of changes in the volume of pleural effusion and speed of accumulation of fluid by chest X-ray as well as more objective values such as levels of LDH, CEA, and glucose and the conversion of positive cytologic characteristics.

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