PHARMACOKINETIC STUDY OF INTRAPERITONEALLY ADMINISTERED ETOPOSIDE AGAINST PERITONITIS CARCINOMATOSA

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Received May 2, 1994

Abstract : Etoposide is becoming important in primary and salvage therapy for ovarian cancer. In the present study, we administered etoposide (100-300 mg/subject) intraperitoneally to six patients suffering from cancerous peritonitis, particularly that resulting from ovarian cancer, to investigate the bioavailability and pharmacokinetics of this drug. The peak etoposide level in the ascites was 80 μg/ml. Twelve hours after intrapertoneal administration (i. p.), more than 10 μg/ml of etoposide was still found in ascites. The serum level after administration of 100 mg i. p. reached approximately 4 μg/ml within 30 minutes, and 1 μg/ml of etoposide was still found in serum after 24 hours. The etoposide levels in ascites and serum after 300 mg i. p. were higher than those after 100 mg i. p. When the peritoneum was intact, the area under the curve (AUC) of etoposide in ascites was low (164 μg • h/ml), and the peritoneal clearance (Clp) was high. In contrast, in advanced cancerous peritonitis, the AUC in ascites was high (500 μg • h./ml) and the Clp was low. The AUC of etoposide in the ascites of patients with cancerous peritonitis was more than five-fold greater than that of patients with an intact peritoneum, while MRT (mean residence time) was 15-fold, and VRT (variance of residence time) was 300-fold greater. The AUC ratio in intact peritoneum was 4.1, and that in cancerous peritonitis ranged from 17.8 to 27.1. AUC, MRT and VRT of etoposide transported into the blood were slightly higher in advanced cases than in those with intact peritoneum. These findings indicate that intraperitoneal etoposide han not only a direct anticancer effect in the abdominal cavity but also shows effects via the vascular system of the tumor.

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Index Terms

etoposide, intraperitoneal (i. p.) chemotherapy, bioavailability, pharmocokinetics, peritonitis carcinomatosa

Abbreviations

AUC : area under the curve, Clp : peritoneal clearance, MRT : mean residence time, VRT : variance of residence time, Kel : the rate of disappearance from the abdominal cavity

INTRODUCTION

To increase the efficacy of anticancer agents, it is important to elevate the drug level at the site of tumor tissues. In particular, introducing anticancer agents directly into the peritoneal cavity of patients with cancerous peritonitis may expose individual free-floating tumor cells as well as small surface tumor nodules to much higher drug levels than those achieved with systemic infusions[1,2]. However, many questions regarding optimal drugs and dosing schedules for intraperitoneal chemotherapy still remain unanswered.

We should be aware of the pharmacodynamics of intraperitoneally administrated drugs and have access to clinical pharmacological evaluations, since individual patients have different clinical conditions.

Recently, etoposide, a semisynthetic podophyllotoxin derivative, has been gaining importance in both primary and salvage therapy for ovarian cancer[3,4], Although it has not yielded universally favorable results as a single agent, it appears to be useful when administered in combination with cisplatin or carboplatin[5,6,7].

In the present study, we administered etoposide intraperitoneally to patients with cancerous peritonitis, particularly that resulting from ovarian cancer. The bioavailability and pharmacodynamics of etoposide were assessed using a two-compartment model and moment analysis. An additional aim of this study was to determine whether concomitant treatment with cisplatin yielded favorable results in the treatment of cancerous peritonitis.

MATERIALS AND METHODS

Patients

Six adult female patients with cancerous peritonitis were studied ; their characteristics are shown in Table 1. All cases had creatinine clearance (Ccr) greater than 80 ml/min., white blood cell (WBC) count greater than 3.000/μl and platelet count greater than $10\times10^4/\mu$l.

Chemotherapy

Patients were treated with a regimen of intraperitoneal administration with etoposide and cisplatinum on a monthly schedule. A maximum of three courses of therapy was delivered, followed by a response evaluation. The starting dose of etoposide was 100 mg/subject and that of cisplatinum was fixed at 50 mg/m^2. In an individual patient, dose escalation of etoposide was permitted up to 300 mg/subject, if disease progression had been demonstrated after standard

induction-treatment with a platimum-based combination chemotherapy. Both agents were administered intraperitoneally as rapidly as possible, and were diluted in 500 ml of physiological saline when ascites was not found and without dilution when considerable ascites(>500 ml)was found via exploratory laparotomy or abdominal punctation.

Samples

Blood samples were taken from a peripheral vein. Ascites samples were taken using an indwelling abdominal drain and were heparinized. Urine specimens were also collected and all samples were frozen at −20℃ until analysis. Samples were drawn before and at 0.25, 0.5, 1, 2, 3, 4, 6, 12, 24 and 48 hours after administration.

Etoposide assay

The etoposide levels in these specimens were measured using high-performance liquid chromatography with a fluorescence detector[8]. These samples were added to 4′-demethylepipodophyllotoxin 9- (4, 6-propylidene-β-D-glucopyranoside) as an internal standard. Extraction was performed with chloroform. The chloroform phase was dried in a vacuum, then redissolved with a 0.25 ml mobile phase [0.02 MKH_2 PO_4 CH_3 CN (57 : 43, v/v)]. This solution was injected onto a column (Senshu Pak ODS-2251-D) and analyzed with a detector (650-10 S, Hitachi Factory Co., Ltd., Tokyo, Japan) using an excitation wavelength of 290 nm and a fluorescence wavelength of 320 nm. The flow-rate retention time for this assay was 7.6 min. and the lower limit of detection for etoposide in plasma was 5 ng/ml.

Pharmacokinetic calculations

Etoposide concentration vs time was evaluated using a nonlinear leastsquares model analysis incorporating a two-compartment model and by moment analysis without a model.

RESULTS

Time-course changes in etoposide levels in the ascites

The time courses of changes in etoposide levels in the ascites and serum after intraperitoneal administration of 100 mg of etoposide in five cases are shown in Fig. 1. The mean levels and standard deviations are shown in Fig. 2. There were some individual variations ; however, relatively high levels in ascites were maintained for about 30 min. after administration, averaging 60 to 80 μg/ml and reaching a maximum of 179 μg/ml.

These levels decreased slowly as more than 10 μg/ml of etoposide was still found in the ascites 12 hours after administration. However, in Case 1, the abdominal fluid diappeared

Table 1. Characteristics of patients receiving i. p. etoposide

Patient No.	Age	Histology		Stage	Ascites(ml)	Dose of etoposide (mg/subject)	Area of body surface (m^2)
1	73	Mucinous*	(Ovary)	I a	No	100	1.36
2	47	Serous Ca.	(Ovary)	IIIc	1500	100	1.55
3	56	Mucinous Ca.	(Ovary)	IIIc	No	100	1.44
4	70	Serous Ca.	(Ovary)	IV	1500	100	1.50
5	61	Pancreas Ca.		IV	3000	100	1.48
6	46	Mucinous Ca.	(Ovary)	IV	1500	300	1.52

* : borderline malignancy

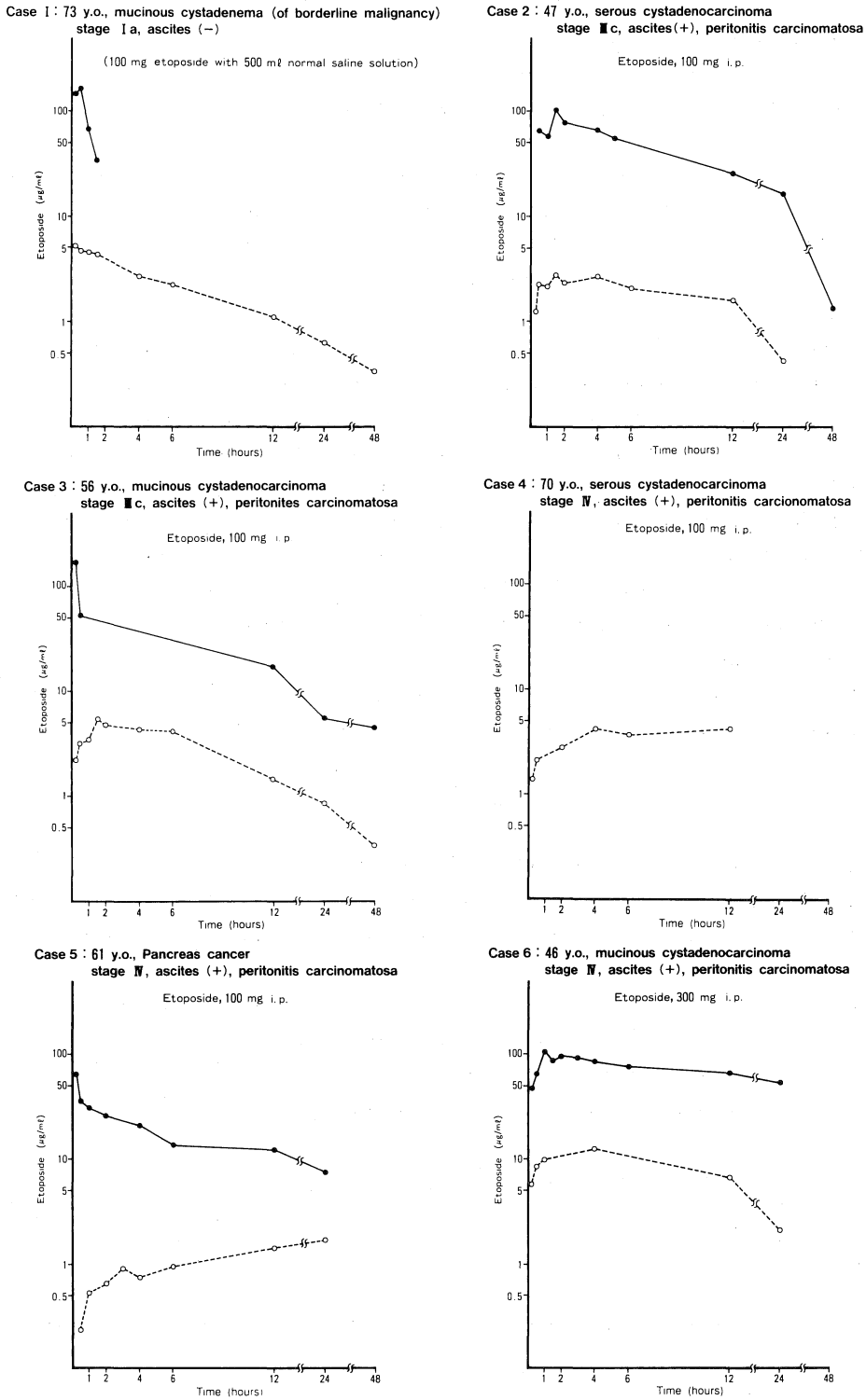

Fig. 1. Cencentration curves of etoposide in ascites and plasma after intraperitoneal administration of etoposide. ●——● : Etoposide in ascites, ○-------○ : Etoposide in plasma.

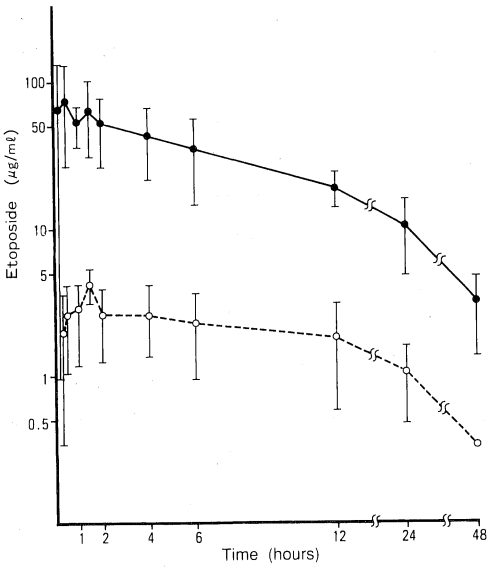

Fig. 2. Concentration curves for etoposide in ascites and plasma after intraperitoneal administration of 100 mg etoposide. The data represent the mean±S. D. for five patients.
●——● : Etoposide in ascites. ○-----○ : Etoposide in plasma.

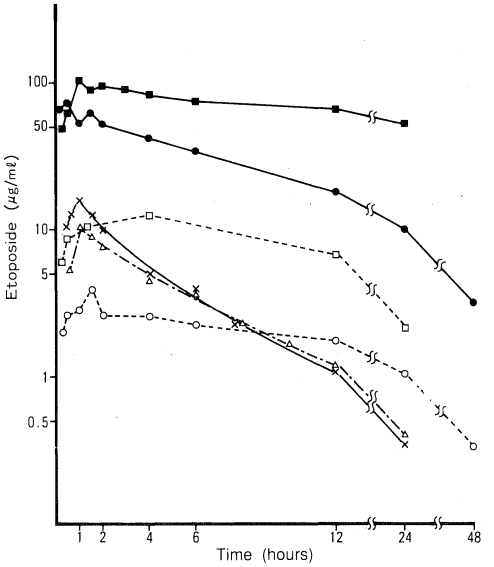

Fig. 3. Concentration curves of etoposide in ascites and plasma.
■—■ : Etoposide in ascites (300 mg i. p.),
●—● : Etoposide in ascites (100 mg i. p.)
□--□ : Etoposide in plasma (300 mg i. p.),
○---○ : Etoposide in plasma (100 mg i. p.)
×—× : Etoposide in plasma (80 mg/m²i. v.)
△---△ : Etoposide in plasma (160 mg/m²p. o.)
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rapidly from the abdominal cavity ; thus, samples could be obtained only up to 90 min.

Etoposide 300 mg i. p. was administered in Case 6. As shows in Fig. 3, the etoposide level in the ascites was notably higher than in the group treated with 100 mg of etoposide. The maximum level 1 hour after administration was 106 μg/ml. More than 50 μg/ml of etoposide was still found in the ascites 24 hours after administration.

Time-course changes in etoposide levels in serum

The transportation of etoposide into the bloodstream after intraperitoneal administration was relatively good (Figs. 1 and 2) ; in Cases 1 and 2, etoposide reached a level of approximately 4 μg/ml in serum at 30 to 40 min. after administration. This level decreased slowly ; 1 μg/ml of etoposide was still found in the blood after 24 hours. However, in Case 4, a maximum of 4 μg/ml of etoposide was maintained in the blood for nearly 12 hours, showing no elimination phase. In Case 5, the serum level of etoposide increased rather slowly up to 24 hours.

When 300 mg of etoposide was administered intraperitoneally (Case 6), transportation into the bloodstream increased. The maximum blood etoposide level observed was 2.5 times more than seen with the 100 mg dose, i. e. 10 μg/ml. This level was maintained for about 4 hours. At twenty-four hours after i. p. administration of 300 mg of etoposide, 2 μg/ml was still found in the blood (Fig. 3).

Analysis using the compartment model

The pharmacokinetics of etoposide in ascites in the six cases, as determined by using the

compartment model, are shown in Table 2. Analyses were based on the two-compartment model, but because the mode of disappearance of etoposide from the ascites was monophasic in Cases 1 and 2, a one-compartment model was applied to these cases.

Generally, intraperitoneally administered drugs show a two-phase elimination pattern (α and β phases) but in this study there was considerable variation among the cases. The half-life in the α phase was 1.4 hours on average, and in the β phase, 29 hours.

When the peritoneum was intact and ascites was not found, as in Case 1, the etoposide level in the abdominal fluid as expressed by the area under the curve (AUC) was lower, 164 μg • h./ml, and the rate of disappearance from the abdominal cavity (Kel) was rapid ; thus, the peritoneal clearance (Clp) was higher.

In contrast, Cases 2, 3, 5 and 6 involved advanced cancerous peritonitis, and etoposide levels in the ascites as expressed by AUC were higher than 500 μg • h./ml. The rate of disappearance from the abdominal cavity in these cases was low, and thus the peritoneal clearance (Clp) was also low.

Moment analysis

These indices were calculated ; the AUC was the zero-order moment, the mean residence time (MRT) was the primary moment, and the variance of residence time (VRT) was the second moment (Table 3).

Table 2. Pharmacokinetic parameters of ascites in six patient receiving i. p. etoposide

Patient	AUC (ug•h/ml)	$t_{1/2\alpha}$ (h)	$t_{1/2}$ (h)	Clp (ml/min)	k_{12} (h-1)	k_{21} (h-1)	Kel (h-1)	V_1 (l)	V_2 (l)	V_{ss} (l)
1 *	164	—	0.40	10.2	—	—	1.75	—	—	0.35
2 *	908	—	7.4	1.39	—	—	0.0934	—	—	1.18
3 **	694	0.11	31.4	2.40	4.90	0.104	1.34	0.11	5.07	5.18
4 ***	—	—	—	—	—	—	—	—	—	—
5 **	521	1.72	17.2	3.20	0.131	0.246	0.0659	2.91	1.55	4.46
6 **	4680	2.30	38.7	1.07	0.0601	0.236	0.0228	1.18	0.30	1.49

* one - compartment model ** two - compartment model *** sample not obtained

Table 3. Pharmacokinetic parameters of i. p. etoposide in ascites and plasma of six patients by moment analysis

Patient		AUC (ug h/ml)	$t_{1/2}$ (h)	MRT (h)	VRT (h_2)	Clp (ml/min)	AUC ratio
1	Ascites	162	0.44	0.81	0.41	10.3	4.1
	Plasma	39.2	10.2	10.4	175	42.5	
2	Ascites	1150	8.2	12.5	126	1.45	27.1
	Plasma	42.4	7.6	11.5	117	39.3	
3	Ascites	1440	105	105	20300	1.16	17.8
	Plasma	81.1	16.3	18.2	485	20.6	
4	Ascites*	—	—	—	—	—	—
	Plasma**	—	—	—	—	—	
5	Ascites	534	17.3	23.2	616	3.12	—
	Plasma**	—	—	—	—	—	
6	Ascites	4880	34.9	50.0	2540	1.14	26.3
	Plasma	185	8.4	12.5	147	27.0	

* sample not obtained

** analysis impossible due to lack of illumination phase

The AUC of etoposide in the ascites of subjects with advanced cancerous peritonitis (Cases 2, 3, 5 and 6) was more than five-fold that of the subject with an intact peritoneum (Case 1), the MRT was more than 15-fold greater, and the VRT more than 300-fold.

AUC, MRT and VRT values for etoposide transported into the blood stream were slightly higher in the cases with cancerous peritonitis than in Case 1. The AUC ratio was 4.1 in Case 1 and ranged from 17.8 to 27.1 in cases of cancrous peritonitis.

Integrated urinary excretion

The integrated urinbry excretion of etoposide after 100 mg intraperitoneal administration is shown in Fig. 4. Twenty-four hours after administration, 30 to 40% of the dose administered had been excreted in urine.

Clinical effect

In the present study, after three cycles of EP therapy (etoposide with cisplatinum), responses were evaluated by the criteria of primary response to chemotherapy for ovarian cancer, authorized by the Japan Society for Cancer Therapy. As for ascites, one case (Case 2) showed complete response (CR) ; two others (Cases 4, 6) demonstrated partial response (PR), and the rest (Case 5) remained no change (NC). However, PR with Case 2 and minor response (MR) with Case 3 were shown with respect to measurable lesions.

DISCUSSION

In many cases, ovarian carcinoma tends to remain limited to the peritoneal cavity throughout most of its clinical course. Therefore, the most important factor in a successful therapeutic strategy for ovarian cancer is control of the disease during its intraperitoneal stage. One effective treatment for ovarian cancer involves the use of intraperitoneal chemotherapy. In this

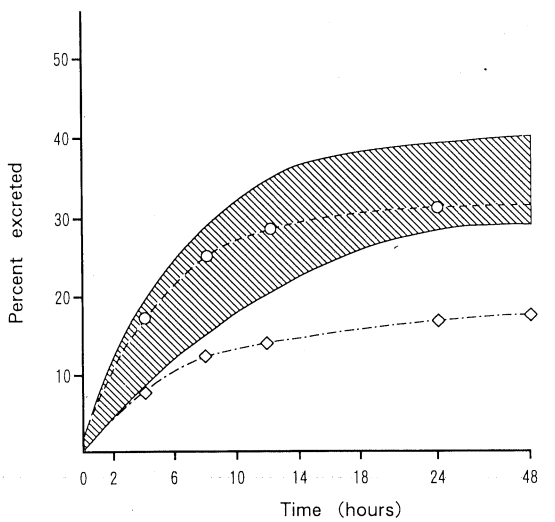

Fig. 4. Urinary excretion of etoposide after i. p., i. v. and p. o. administration.
▨ : 100 mg i. p.
○------○ : 100 mg/m²i. v.
◇-·-·-·-◇ : 160 mg/m²p. o. Pfeffer, M. et al. 1987

regard, intraperitoneal administration of cisplatinum (CDDP) has proved to be effective, and the pharmacokinetics of this drug have been well documented[9,10,11,12].

Etoposide is a semisynthetic glycoside of podophyllotoxin, an extract of the plant *Podophyllum*, that is effective as a second-line drug for refractory ovarian cancer[3,4]. As for a phase I-II study of combination chemotherapy with intraperitoneal cisplatin (90 mg/m^2) and systemic etoposide in advanced ovarian cance, the recommended dose of etoposide was reported to be 600 mg/m^2[2,13]. In our clinical trial, the dose of etoposide was defined to be 100 mg/subject and escalated to 300 mg/subject in an individual case, considering the sufficient safety margin of intraperitoneally administered etoposide. It is usually administered orally or intravenously and there is little information regarding its effects after intraperitoneal administration[14,15].

In the present study, we administered etoposide intraperitoneally to patients with cancerous peritonitis, and investigated the pharmacokinetics of the drug.

There were some individual variations, but generally the highest level of etoposide in the ascites (100 μg/ml) was obtained immediately after 100 mg i. p. administration. The level was more than 1 μg/ml until 48 hours after administration.

Transportation in to the bloodstream via the intraperitoneal route was also good. The maximum serum level was 5 μg/ml. Twenty-four hours after administration, the serum level of etoposide was still 1 μg/ml.

In this study, only total etoposide levels were measured. Free etoposide (the active anticancer form) was not measured ; however, a high intraperitoneal concentration of etoposide after 100 mg i. p. seems to be sufficient to kill free malignant cells directly in the abdominal cavity. The anticancer effect via the vascular system of the tumor after 100 mg i. p. administration, as shown in Fig. 3, must be comparable to the effects after intravenous or oral administration[16].

The considerable variation in ascites and serum concentration observed among the cases may be a result of the stage of cancerous peritonitis. When the peritoneum was intact and there was no ascites, the Kel of etoposide from the abdominal cavity was large and Clp was high, indicating good transportation of etoposide into the bloodstream. Consequently, the AUC of etoposide in peritoneal fluid was low.

In contrast, in cases of advanced cancerous peritonitis, the transportation of etoposide into the bloodstream was distributed by the presence of ascites and a thickened peritoneum ; thus, the Kel of etoposide from the abdominal cavity and the Clp were low. Therefore, the AUC of etoposide in the ascites in advanced cancerous peritonitis was large and the anticancer effect of the drug in the abdominal cavity was intensified. In more advanced cases, the elimination phase of etoposide in blood was not observed ; therefore, the AUC of serum etoposide was also increased. This observation not only indicates a good effect via the vascular system, but also a reduced potential for side effects such as bone-marrow suppression.

The AUC ratio represents ascites AUC/blood AUC. Drugs with a higher AUC ratio are considered to be more suitable for intra-abdominal administration[17]. In the present study, the AUC ratio of etoposide in the intact peritoneum was low(4.1), even in cancerous peritonitis (17.8-27.1).

Thus, etoposide may not be suitable for intraperitoneal administration. However, the low AUC ratio indicated not only a direct effect in the abdominal cavity but also an effect via the vascular system.

The anticancer effect of etoposide is apparently limited ; thus, simultaneous administration of CDDP should yield a synergistic effect. In this study, we administered both CDDP and etoposide intraperitoneally. This combination yielded a partial response in resistant and recurrent cases. Thus, etoposide may be useful as a second-line drug for treating recurrent cancerous peritonitis. Nevertheless, the reason why no reponses were shows in pancreatic cancer (Case 5) seemed to depend upon its primary sensitivity to anticancer agents. At this time, there is no effective single agent or combination chemotherapy program for pancreatic cancer, and progress will depend upon the development of newer agents.

Etoposide is a cell-cycle phase-specific drug, and the magnitude of its effect therefore relies on the duration of exposure above a certain concentration[18,19]. In small-cell lung cancer, the clinical effect of etoposide is largely dependent on long-duration exposure to more than 1 μg/ml of the drug. An administration schedule that accounts for this fact is therefore necessary[20,21]. Thus, the most effective schedule for intraperitoneal administration of etoposide may be 100 mg/day i. p. for five days, rather than a one-shot bolus intraperitoneal administration.

We are now investigating the effect of continuous intraperitoneal administration of etoposide for five days. More clinical experience is required to establish the efficacy of intraperitoneal administration of etoposide.

ACKNOWLEDGEMENT

The technical assistance of the Nippon Kayaku Co., Ltd. (Tokyo, Japan) is gratefully acknowledged.

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