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Phase I and pharmacokinetic study of intraperitoneal thioTEPA in patients with ovarian cancer

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Summary. A total of 15 patients with residual ovarian cancer confined to the peritoneal cavity after first-line systemic chemotherapy were treated with triethylene-thiophosphoramide (thioTEPA) in a phase I study. A total of 50 courses of thioTEPA were given intraperitoneally in doses ranging from 30 to 80 mg/m^2. The dose limiting toxicity was myelosuppression, which occurred at 80 mg/m^2 and was frequently prolonged. Short-lived nausea and vomiting was easily controlled, and there was no local toxicity. Three patients remain free of disease progression at 6, 6 and 12 months. ThioTEPA concentrations were measured by gas chromatography. Peritoneal fluid concentrations declined rapidly in a first-order fashion, with a half-life of 0.96 ± 0.1 h. A mean of 93% of the drug was absorbed during the 4-h dwell time. Peak plasma levels were achieved 30–60 min after drug instillation and were substantially lower than corresponding peritoneal levels. A pharmacokinetic advantage for intraperitoneal delivery was detected for peak drug concentration (24.9 ± 8.5) and AUC (9.2 ± 4.8). Based on this study, the recommended dose for intraperitoneal thioTEPA is 60 mg/m^2 every 3–4 weeks. However, the rapid absorption of this drug from the peritoneum, secondary to thioTEPA's small molecular weight and lipophilic nature, suggests that it has only a limited role in intraperitoneal therapy.

Introduction

The two major advances in the management of advanced epithelial ovarian cancer, adequate tumour debulking surgery [7] and platinum-based combination chemotherapy, have resulted in significant improvements in response rates. Complete clinical response rates of 40%–50% and pathological complete remission rates of 20%–30% have been reported [5, 15]. However, the overall 5-year survival has remained unchanged for the last 10 years at 10%–15% [12, 16].

The majority of patients with advanced ovarian cancer, including those who achieve pathological complete remission after systemic chemotherapy, eventually relapse with disease confined to the peritoneal cavity. The concept of intraperitoneal regional chemotherapy [6, 14] recognises the potential of the peritoneum to act as a semi-permeable membrane for drug diffusion. The delivery of chemotherapy directly into the peritoneal cavity would create higher drug concentrations locally than could be achieved by systemic administration and, therefore, potentially increase tumour cytotoxicity. Systemic toxicity would be decreased secondary to lower plasma concentrations of the drug. Alternatively, very high concentrations of drug could be delivered locally, yet diffusion into the systemic circulation would enable the same plasma drug levels to be achieved as with conventional intravenous drug delivery [17]. The ideal drug for intraperitoneal administration should, in theory, have a low peritoneal clearance, as determined by the size of the drug and its molecular characteristics [6]. Intraperitoneal chemotherapy offers an attractive concept for consolidation therapy in patients with ovarian cancer who achieve pathological complete remission or microscopic/minimal residual disease after completing systemic chemotherapy. In addition, it may be useful as adjuvant therapy in women with stage I ovarian cancer.

Triethylene-thiophosphoramide (thioTEPA) is an alkylating agent whose activity against ovarian cancer has been demonstrated in clinical studies [20]. In vitro studies using an A-2780 cell-line (Ozols, NCI) ovarian spheroid model to mimic free-floating ascitic cells have shown that exposure to thioTEPA levels of >10 μg/ml for 1 h causes significant growth delay (J. Cassidy, personal communication).

ThioTEPA has characteristics that make it theoretically suitable for intraperitoneal use. It is not known to have vesicant properties and has been used in the past for intracavitary administration [2] without causing local toxicity. Previous intraperitoneal therapy with thioTEPA, apart from that in a recent study [21], has involved administra-

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Table 1. Patient characteristics

Number of patients	15
Age (median) in years	60
(range)	40–65
Prior chemotherapy:	
Carboplatin ± chlorambucil	13
Cisplatin ± cyclophosphamide	2
Residual disease bulk:	
<2 cm	9
>2 cm	6
(including 3 patients with ascites)	

tion of the drug in small volumes of fluid only, which does not provide uniform peritoneal distribution and therefore compromises potential cytotoxicity. We conducted a phase I study to determine the maximum tolerated dose of thioTEPA given intraperitoneally, to assess local and systemic toxicity, and to investigate the possibility of a pharmacokinetic advantage for this method of delivery.

Patients and methods

Patient selection. Patients with histologically confirmed ovarian carcinoma confined to the peritoneal cavity were eligible for this study. All patients had previously received treatment with first-line systemic chemotherapy comprising either carboplatin- or cisplatin-based combinations. Patients assessed clinically and radiologically as being in complete remission after completion of this chemotherapy underwent second-look laparotomy where residual disease was categorized as being either minimal (tumour diameter, <2 cm) or bulk (tumour diameter, >2 cm) disease. In three patients with advanced disease, treatment was given to control recurrent ascites. Other eligibility criteria included suitability for placement of a Tenckhoff peritoneal dialysis catheter; adequate bone marrow reserve, defined as hemoglobin (Hb) values of >10 g/l, a WBC count of $>4 \times 10^9$/l, and a platelet count of $>100 \times 10^9$/l; adequate renal (serum creatinine, <130 μmol/l and hepatic (serum bilirubin, <20 μmol/l) function, and informed consent.

Treatment plan. Tenckhoff dialysis catheters were placed in the peritoneal cavity of patients under direct vision at laparotomy. Following surgery, the catheter was continuously infused with normal saline at 20 ml/h for 7 days to prevent adhesion formation at the catheter tip and therefore decrease the risk of outflow obstruction. Patients were instructed in the care of the catheter. Between the 7th and 10th post-operative days, peritoneal fluid distribution was assessed by isotope scanning after intraperitoneal delivery of human serum albumin labelled with technetium Tc 99m (^{99}Tc-HSA) in 2 l normal saline.

Patients were treated with thioTEPA (Lederle Laboratories, Hampshire UK), given intraperitoneally in 2 l prewarmed normal saline at 37° C. In patients with ascites, the fluid was drained prior to administration of thioTEPA. The total dose of drug was initially delivered in 500 ml dialysate, and a further 1,500 ml of fluid was then instilled. The total 2-l volume was given over 20 min. The fluid was left to dwell in the peritoneum for 4 h and then drained, when possible, completely.

The starting dose of thioTEPA (30 mg/m^2) was based on previous experience for intracavitary therapy with this drug [2]. Escalation of dose within patients was permitted in the absence of significant toxicity (WHO grade of <2) from the previous course. Doses were escalated until the maximum tolerated dose, defined as WHO toxicity of grade 4 or prolonged grade 3, was attained, at which dose a minimum of three extra patients were treated. Treatment was given on a 3- to 4-week schedule. The treatment interval was dependent on WBC and platelet counts and was delayed if the WBC count was $<3 \times 10^9$/l and platelets amounted to $<100 \times 10^9$/l on the planned day of therapy. A maximum of six courses was given.

Clinical pharmacologic studies. Serial blood samples were collected in a heparinized tube at 0, 5, 10, 20, 25, 30, 60, 90, 120, 180 and 240 min and at 6, 8, 12 and 24 h, with time 0 representing the beginning of drug instillation. Each sample was centrifuged immediately (1,000 rpm for 10 min). Serial peritoneal fluid samples (10 ml) were collected via the peritoneal catheter at 20, 25, 30, 60, 90, 120, 180 and 240 min, with time 20 representing the end of drug instillation. Plasma and peritoneal fluid samples were stored at –20° C until analysis.

Sample extraction and analysis. The extraction of thioTEPA from plasma and peritoneal fluid was based on the method described by Grochow et al. and other workers [4, 8, 21]. In brief, 0.4 ml plasma or 0.1 ml peritoneal fluid was vortexed for 20 min in 15 ml tapered gas centrifuge tubes with 2 ml HPLC-grade ethyl acetate (BDH Poole, UK) containing 50 μg/ml diphenylamine (Fluorochem, Glossip, UK) as an internal standard. The sample extracts were then centrifuged at 2,000 rpm for 5 min and the organic phase was removed and transferred to 2-ml smoked-glass sample vials prior to analysis. Then, 2 μl acetate extract was injected into a Carlo Erba Fractovap series 2350 Gas Chromatograph, fitted with a 2 m × 3.5 mm (inside diameter) glass column containing 3% OV 225 on 100- to 120-mesh Supelcoport (Phase Sep, Deside, UK).

Temperature conditions were: column oven, 202° C; injector, 250° C; and detector temperature, maintained at 250° C. Gas flow rates were: carrier (nitrogen), 30 ml/min; flame gases (hydrogen/air), 35 and 200 ml/min, respectively. The detector was nitrogen-phosphorous selective and gave a linear response to thioTEPA over a wide enough concentration range for the purposes of this study. The limit of sensitivity was 5 ng/ml (standard solution). The above conditions enabled good resolution of thioTEPA from the internal standard with no interference from endogenous material. Retention times for thioTEPA and diphenylamine were 2.4 and 2.8 min, respectively. Integration of peak areas was carried out on a PYE Unicorn DP88 minigrator (Scotlab, Bellshill, UK). ThioTEPA concentrations were calculated by least-squares linear regression analysis, based on peak area ratios. Calibration data were obtained individually for each patient run by the inclusion of spiked plasma/peritoneal fluid standards with every sample batch. The linearity of the extraction was maintained throughout the patient study, with correlation coefficient values (r) that were never lower than 0.998.

The extraction of TEPA was attempted using the above method, substituting chloroform for ethyl acetate as the extracting solvent. As this technique was unsatisfactory, further analysis was carried out using C18 extraction cartridges [4].

Pharmacokinetic analysis. The area under the plasma concentration curve (AUC) was calculated using the log trapezoidal rule from time 0 to the last measured time point, and then extrapolated from the last time point to infinity. The AUC for peritoneal fluid was calculated in a similar way except that the duration was only 4 h, corresponding to actual dwell time. For the purposes of calculating thioTEPA absorption, it was assumed that the total volume of peritoneal fluid remained unchanged over the dwell time. One- and two-compartment models, corrected for the appropriate infusion model, were evaluated for "goodness of fit" for plasma and peritoneal concentration data, using an "in-house" programme based on the Marquhandt algorithm.

Results

A total of 15 patients received a total of 50 courses of intraperitoneal thioTEPA at doses ranging from 30 to 80 mg/m^2. Four patients completed six courses of treatment. The patient characteristics are shown in Table 1. The Tenckhoff catheters were generally well tolerated. There were no serious operative complications or episodes of bacterial peritonitis. Two patients developed wound infections at the catheter exit site, but these resolved with appropriate antibiotic therapy. There was one episode of inflow

Table 2. Haematological toxicity

Dose (mg/m²)	Patients (*n*)	Courses (*n*)	Nadir WBC (× 10⁹/l): median (range)	Nadir platelets (× 10⁹/l) median (range)
80[a]	9	18	1.9 (0.7–2.8)	62 (9–166)
60	7	16	2.2 (1.8–2.5)	108 (74–219)
50	3	5	2.3–4.0	135–175
45[b]	2	4	5.7	185
40[b]	1	4	2.6	119
35[b]	1	2	4.9	180
30[b]	1	1	3.5	306

[a] Doses of 5 patients treated at 80 mg/m² were reduced to 60 mg/m² due to treatment delay secondary to myelosuppression

[b] At lower doses, nadir counts were not always available

obstruction secondary to progressive tumour obstructing the catheter. In five patients, peritoneal fluid did not drain completely (outflow obstruction – retained fluid: 500 ml–1 l, three patients; >1 l, two cases). The fluid was absorbed systemically and did not preclude further treatment. In all patients, the pre-treatment intraperitoneal perfusion scans demonstrated good distribution of fluid throughout the peritoneal cavity.

The dose-limiting toxicity of intraperitoneal thioTEPA was myelosuppression, which occurred at 80 mg/m². Haematological toxicity is detailed in Table 2. Five patients had WBC toxicity of grade 3 (WHO) and one had grade 4; 3 patients had platelet toxicity of grade 3 (WHO) and one had grade 4. There were no septic or bleeding episodes during the study. One interesting aspect of the myelotoxicity was the prolonged period of myelosuppression that occurred particularly after repeated treatments at the higher dose levels. On occasions, marrow recovery occurred only after 6 or 7 weeks. At 80 mg/m² the median interval for recovery was 39 days. This resulted in treatment delays, and the dose of five patients initially treated at 80 mg/m² was reduced to 60 mg/m². This phenomenon was cumulative and may be related to a direct myeloproliferative stem-cell effect by thioTEPA. There was no relationship between the degree of myelotoxicity related to thioTEPA and any myelotoxicity attributable to previous systemic chemotherapy. There was no other significant toxicity with thioTEPA. Nausea and vomiting were always mild (WHO grade of <2), short-lived and easily controlled with simple anti-emetics. There were no episodes of clinical chemical peritonitis.

Response data

This was a phase I study and the majority of patients did not have measurable or evaluable disease; thus, the end point for response evaluation was assessed as being clinical disease progression. Three patients, all with tumour bulk of <0.5 cm, remain free from disease progression at 6, 6 and 12 months after commencing therapy. In patients with tumour bulk of <2 cm, the median progression-free interval was 6 months, whereas this interval was only 2 months in patients with bulky residual disease. In the three patients with recurrent ascites, thioTEPA was effective in controlling the rate of ascites formation, although peritoneal washings remained positive for malignant cells.

Pharmacokinetics

The pharmacokinetic data are summarised in Table 3. Peak peritoneal thioTEPA concentrations were achieved immediately or within 30 min of completion of drug instillation. This delay in reaching peak levels may be explained by uneven mixing of thioTEPA and dialysate in the early stage of the peritoneal distribution phase. Peritoneal fluid concentrations declined in a first-order fashion, with a $t^1/_2$ of 0.96 ± 0.1 h (mean ± SEM). Thiotepa was absorbed rapidly from the peritoneal cavity, with absorption being almost complete at the end of the 4-h dwell time (mean absorption, 93% ± 2%) and did not vary with dose (Fig. 1).

In keeping with the rapid fall in peritoneal thioTEPA levels, peak plasma concentrations were achieved within 30–60 min of completion of the intraperitoneal instillation and then declined over an 8- to 12-h period. Linear regression showed a direct correlation between the thioTEPA dose delivered and the peak peritoneal and plasma concentrations (P <0.006). At all dose levels except 60 mg/m², plasma thioTEPA declined in a biexponential fashion, with $t^1/_2\alpha$ representing the distribution phase and $t^1/_2\beta$, the elimination phase. At 60 mg/m² the $t^1/_2\alpha$ could not be measured, although there was no obvious difference in the rate of decline of plasma thioTEPA between this dose and others (see Table 3). The pharmacokinetic plasma-concentration data were fitted to an oral first-absorption, two-compartment model based on the Marquhandt algorithm. Peak plasma levels measured at doses of 60–80 mg/m² were similar to those obtained for "standard" (20–30 mg) intravenous doses of thioTEPA [9].

Table 3. Pharmacokinetic data for all dose levels

Thiotepa dose	Patients (*n*)	Mean peak i.p. concentration (μg/ml)	Mean peak plasma concentration (μg/ml)	Mean peritoneal AUC (μg ml⁻¹ h)	Mean plasma AUC (μg ml⁻¹ h)	Mean peak concentration P-K advantage	AUC peritoneal / AUC plasma	Peritoneal $t^1/_2$ (hr)	Plasma $t^1/_2$ (hr) α	Plasma $t^1/_2$ (hr) β	% absorption
80 mg/m²	8	21.5 ± 5.2	0.78 ± 0.26	26.8 ± 4.2	2.7 ± 1.0	27.5 ± 7.1	11.1 ± 5.0	0.95 ± 0.1	1.6 ± 0.3	3.7 ± 0.4	93 ± 3
60 mg/m²	3	11.9 ± 3.9	0.52 ± 0.1	14.9 ± 5.1	2.5 ± 0.5	20.0 ± 9.7	5.8 ± 1.4	0.85 ± 0.2		2.6	92 ± 3
50 mg/m²	1	7.1	0.45	7.8	1.6	16.6	4.9	0.9	1.2	2.3	95
40 mg/m²	1	6.7	0.38	5.7	0.9	17.5	5.7	0.8	1.5	3.5	97
35 mg/m²	1	4.2	0.18	7.2	0.8	24	8.9	1.3	1.5	4.6	90

All data represent mean values ± SEM. P-K, pharmacokinetic

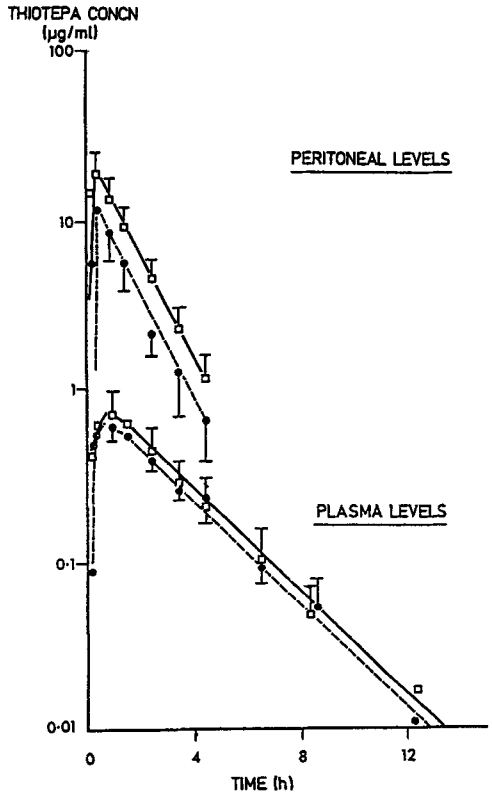

Fig. 1. Plasma and peritoneal concentration-time relationship for thioTEPA doses of 60 (●----●) and 80 mg/m² (□——□) (mean ± SEM)

A pharmacokinetic advantage was demonstrated for the intraperitoneal administration of thioTEPA. At 80 mg/m², the mean peak peritoneal concentration was 27.5 times (range, 19–43 times) greater than the mean peak plasma concentration, and a similar concentration gradient was detected at all dose levels. This regional delivery advantage was also expressed for the AUC (mean, 9.2 ± 4.8). There was no correlation between nadir WBC or platelet counts and either peak plasma or plasma AUC levels. Also, there was no correlation between the duration of nadir blood counts and plasma AUC.

Although it is possible that the metabolism of thioTEPA to TEPA may form a major mechanism for thioTEPA clearance, we could not detect TEPA in any plasma or peritoneal fluid samples. This may be related to various factors, including the known instability of TEPA when stored for prolonged periods and the lack of an effective standard for analysis.

Discussion

Various antineoplastic agents, given intraperitoneally, have been investigated in phase I and II trials, including Adriamycin [17], cisplatin [10], mitozantrone [1], fluorouracil [18], teniposide [3], etoposide [22] and mitomycin [13]. In terms of disease-free intervals, cisplatin given either alone or in combination has yielded the most promising results for small-volume disease [10], but with associated toxicity, including nephrotoxicity and neurotoxicity, which may be additive if the patient has previously been given cisplatin systemically. Other drugs have been associated with dose-limiting local toxicity [1, 17].

The results of the present study indicate that intraperitoneal thioTEPA is well tolerated. Myelosuppression was the only significant form of systemic toxicity, being ultimately dose-limiting at 80 mg/m². There was no evidence of local peritoneal toxicity.

The pharmacokinetic behaviour of intraperitoneal thioTEPA explains the disappointing response data, with the median progression-free interval being only 6 months in the best prognostic group. Although a pharmacokinetic advantage for intraperitoneal delivery was demonstrated, this advantage was offset by the rapid loss of thioTEPA from the peritoneal cavity. This result had been predicted from an experiment detailing the rate of absorption of different antineoplastic drugs from the peritoneal cavity of rats [11], and this rate of loss is much greater than that described for other cytotoxic agents in the phase I studies referred to previously.

The rapid fall in peritoneal thioTEPA levels explains the relatively small AUC advantage, when compared with the peak level advantage for intraperitoneal thioTEPA, as the AUC advantage is directly influenced by thioTEPA residence time within the peritoneal cavity. Although the plasma concentrations of thioTEPA achieved for intraperitoneal doses of 60 and 80 mg/m² doses were similar to those obtained using standard intravenous thioTEPA doses [9], the impact of intraperitoneal delivery is diminished locally because of the brief drug exposure in the peritoneum. The circulating systemic thioTEPA may be expected to have some effect on the peritoneal tumour, but this may be influenced by the relatively avascular nature of these deposits. The rapid loss of thioTEPA from the peritoneum can be explained by the molecular characteristics of the drug, specifically its low molecular weight (188 kDa) and lipophilic nature. Furthermore, the loss from the peritoneum is likely to be secondary to absorption of thioTEPA into the general circulation rather than to chemical decomposition or metabolism of thioTEPA to TEPA within the peritoneal cavity [21]. The results of our study involving both toxicity and pharmacokinetics are similar to those obtained by Wadler's group [21], although the latter authors could not determine any correlation between the dose of thioTEPA delivered and the peak intraperitoneal and plasma thioTEPA levels. This correlation was significant in our study and was not affected in patients with residual ascites that required drainage prior to thioTEPA administration.

For a drug to be effective for intraperitoneal delivery, it should not require processing or metabolism to an active state. Although there is little knowledge of thioTEPA's metabolism in humans, recent work [19] has suggested that the cytotoxic effect of this drug may at least partly be dependent on its metabolic activation by the hepatic cytochrome P-450 enzyme system. This may further explain the disappointing therapeutic results obtained in the present study.

The inability to detect TEPA in plasma and peritoneal samples was probably related to difficulties in chemical analysis, including the lack of a stable internal standard and the chemical instability of TEPA, rather than an actual

lack of the metabolite in the samples. Wadler et al. [21] noted earlier and quantitatively more significant levels of TEPA in plasma than in peritoneal fluid, suggesting that the conversion of thioTEPA to TEPA had occurred outside the peritoneum. However, it remains very unclear as to how much of thioTEPA's anti-tumour activity is related to TEPA, as there is a wide variation in the in vitro cytotoxicity of thioTEPA and TEPA [19].

Based on the outcome of this study, the recommended dose of intraperitoneal thioTEPA is 60 mg/m^2, given every 3–4 weeks. As this treatment was effective in controlling ascites reaccumulation in three patients and was extremely well tolerated by patients, intraperitoneal thioTEPA may be useful for palliation of recurrent malignant ascites. However, due to the drug's molecular characteristics and, hence, rapid absorption from the peritoneal cavity, it has a limited role as a form of consolidation therapy for ovarian carcinoma.

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