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Escalating Dose Regimen of Intraperitoneal Mitoxantrone: Phase I Study—Clinical and Pharmacokinetic Evaluation

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Abstract—*Mitoxantrone, a recent anthracenedione derivative, is a potentially useful drug for direct intraperitoneal (i.p.) application because of its high tissue binding and therapeutic index.*

We have carried out studies to establish maximum tolerated doses as well as pharmacokinetic studies with i.p. mitoxantrone in 21 patients (5 male, 16 female) with gastrointestinal (9), ovarian (6), unknown (2) and other (4) primary cancers and peritoneal carcinomatosis. Increasing doses (10–40 mg/m^2) were given i.p. every 4 weeks. Five partial remissions (2–8+ months) and 7 stable disease courses (2–6+ months) were achieved. A reduction or disappearance of ascites was seen in an additional 3 patients. Severe toxicity (leucopenia) was observed in 4 patients only after 35 and 40 mg/m^2 i.p.

Pharmacokinetic analysis using high performance liquid chromatography yielded the following data: The mean ratio of area under curve peritoneal fluid to plasma was 1109. The peritoneal clearance rate was 680 ml/min and the mean disappearance half life was 13.1 h. Mean urinary excretion within 24 h was 0.42% of the i.p. dose. These data indicate that mitoxantrone is sequestered in the intraperitoneal tissue compartment and only slowly released.

Based on the outcome of this phase I study we recommend phase II studies at a dose of 30 mg/m^2 i.p., repeated every 3–4 weeks.

INTRODUCTION

DIRECT INTRAPERITONEAL (i.p.) administration of anticancer drugs was introduced in order to achieve tumouricidal drug levels locally while minimizing systemic side-effects of cytostatics. Favourable clinical results have been reported with i.p. cisplatin, mitomycin C and 5-FU [1–3].

Mitoxantrone, an anthracenedione derivative, has shown cytotoxic effects in *in vitro* systems including ovarian and gastrointestinal tumour cell lines [4–6]. Clinical studies with intravenous mitoxantrone have shown favourable results in patients with breast cancer [7–9], lymphoma [10, 11] and leukemia [12–14]. Alberts *et al.* [15] have administered mitoxantrone intraperitoneally in doses of up to 23 mg/m^2. No severe systemic toxicities were observed in contrast to i.v. administration of comparable doses.

In a phase I trial we have administered mitoxantrone intraperitoneally in increasing doses of 10–40 mg/m^2 to 21 patients with ovarian, gastrointestinal, other or unknown malignancies and peritoneal carcinomatosis. The aim of the study was to establish the dose-limiting toxicity of i.p. mitoxantrone and to obtain detailed pharmacokinetic data on mitoxantrone administered via the i.p.route.

MATERIALS AND METHODS

Patients

Twenty-one patients (5 male/16 female) with pathologically proven advanced cancer and peritoneal carcinomatosis entered the study. The presence and extent of peritoneal carcinomatosis was diagnosed by laparotomy or laparoscopy. Nine patients had gastrointestinal cancers. Six patients had ovarian cancers resistant to prior systemic chemo-

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Table 1. Demographic data

Patient	Age	Sex	WHO*	Site of primary cancer	Mass of tumour†	Carcinomatosis + distant metastases	Mitoxantrone doses (mg/m²)
1	64	F	1	Pancreas	A	Yes	10,25,30, 35,40,40
2	77	M	2	Colon	A	Yes	20
3	56	F	2	Gastric	A	Yes	20,25,30,35
4	71	F	0	Ovary	A	Yes	20,25,15
5	63	F	2	Gastric	A	No	20
6	63	F	0	Colon	A	No	20,25,30
7	43	M	2	Colon	A	No	30
8	72	F	2	Ovary	A	No	15
9	57	F	0	Ovary	A	No	20,25
10	46	M	0	Bile duct	A	No	20,20,30,35
11	47	F	1	Ovary	A	No	25,30,35
12	47	F	0	Colon	B	Yes	30,30
13	69	F	0	Colon	B	No	30
14	60	F	1	Ovary	A	No	30
15	52	M	2	Unknown	B	No	30
16	66	F	1	NSCL	B	Yes	30,30
17	58	F	2	Unknown	B	No	30
18	46	F	0	Breast	A	Yes	30,30,30,30
19	53	M	1	Mesothelioma	B	No	30,30,40,40
20	38	F	1	Breast	B	Yes	20
21	60	F	2	Bile duct	A	No	30

*WHO performance status.
†A = macroscopic disease (tumour > 2 cm); B = minimal residual disease.

therapy. Six patients had other tumours or unknown primary cancers.

The study protocol was approved by the institutional review committee. Written informed consent was obtained from all patients before the study.

Patient characteristics are given in Table 1.

Inclusion and exclusion criteria

Patients with a progressive stage of cancer were entered in the study; they must have had a diffuse histologically or cytologically verified peritoneal carcinomatosis. Life expectancy was at least 3 months. Performance status according to WHO criteria [16] was level 2 or better. Previous chemotherapy or extraperitoneal metastases were not reasons for exclusion.

Patients with plasma bilirubin and plasma creatinine above 2 mg/100 ml, white blood cell count below 3000/mm^3 and platelet number below 100,000/mm^3 were excluded. Patients with detectable heart disease and patients who have received more than 350 mg/m^2 of adriamycin i.v. were also excluded.

Treatment and regimen

All patients received i.p. chemotherapy with increasing doses of mitoxantrone (Novantrone™ Cyanamid, Wolfratshausen, F.R.G.). Individual dosages are given in Table 1. It was intended to increase the dose 5 mg/m^2 every 4 weeks with each treatment cycle unless the proceeding dose level evoked grade 3 or 4 toxicity (WHO). Immediately before i.p. mitoxantrone infusion all peritoneal effusion was drained as completely as possible.

Mitoxantrone was diluted in 2 l of Ringer solution (37°C). The drug was infused rapidly with the aid of a previously inserted Port-a-cath™ (Pharmacia, Uppsala, Sweden) and remained i.p. for 24 h before drainage. Access to the reservoir of the Port-a-cath was via an 11-gauge Huber™ needle (Pharmacia, Uppsala, Sweden) percutaneously after careful antiseptic preparation of the overlying skin. Alternatively a PigTail Cordis™ Catheter (Cordis GmbH, Erkrad, F.R.G.) was inserted percutaneously. Correct distribution of fluid in the peritoneal cavity was asserted prior to drug infusion by injection of a small volume of radio-opaque substance (Angiographin™, Schering, Berlin, F.R.G.) and X-ray study.

Clinical evaluation

1. Before each cycle the patients had a complete medical history and physical examination, ECG and chest X-ray. Pretreatment laboratory tests included complete blood counts, liver and renal function tests, coagulation profile and electrolytes. Additional blood counts were done 14 days after each treatment. Whenever ascites fluid could be drained, cytologic analyses were performed. All patients had either repeated ultrasonic or c.t. scan of the abdomen.

2. Side-effects were graded according to WHO criteria [16].
3. Response definition:

Complete remission: Disappearance of all clinical evidence of active tumours for a minimum of 2 months.

Partial remission: Fifty per cent or greater decrease in the sum of the products of all diameters in measured lesions. No simultaneous increase in size of any lesion or appearance of any new lesions.

Stable disease: Steady state or response less than partial remission or less than progression. No appearance of new lesions and no worsening of the symptoms.

Progression: Unequivocal increase of at least 50% in the size of any measurable lesion, and/or appearance of new lesions.

Pharmacokinetic studies

Blood samples (heparinized tubes) were taken before treatment and at 1, 2, 4, 8, 24 h after the end of infusion. Ascites samples were taken from the access port at the same time as blood samples. All samples were centrifuged immediately and plasma and ascites were frozen at −80°C until analysed.

Total urine (24 h portions) was collected during the patients' stay in the hospital. Two hundred and fifty millilitres of double distilled water was added to the urine portions to prevent precipitation.

Mitoxantrone concentrations in plasma and peritoneal fluid were measured by high pressure liquid chromatography (HPLC). The method, equipment and sample preparation have recently been described in detail [17]. Individual mitoxantrone concentration curves were computed by nonlinear least-square regression analysis of all available data, using the TOPFIT program [18]. This computer-based iterative curve fitting program provides an estimate of the area under the curve (AUC), clearance, volume of distribution (VD) and half-life. Pharmacokinetic parameters are given if the coefficient of correlation was >0.9.

RESULTS

Clinical results

Twenty-one patients entered the study, 47 treatment cycles were administered i.p., 44 cycles were evaluable for toxicity. Individual dose schedules are given in Table 1.

Table 2. Side-effects of i.p. mitoxantrone, 10–30 mg/m²

	38 cycles in 15 patients WHO grade				
	0	1	2	3	4
Local	35	2	1	0	0
Nausea	20	16	2	0	0
Diarrhoea	35	0	1	2	0
Bilirubin	36	1	1	0	0
Alkaline phosphatase	36	2	0	0	0
Haemoglobin	34	2	2	0	0
Leucocytes	38	0	0	0	0
Platelets	37	1	0	0	0
Pulmonary	35	3	0	0	0
Fever	36	2	0	0	0
Hair loss	36	2	0	0	0
Pain	29	3	6	0	0
Consciousness	36	2	0	0	0
Neurotoxicity	38	0	0	0	0
Chemoperitonitis	38	0	0	0	0

Table 3. Side-effects of i.p. mitoxantrone 35–40 mg/m²

	6 cycles in 4 patients WHO grade				
	0	1	2	3	4
Local	5	0	1	0	0
Nausea	1	3	2	0	0
Diarrhoea	4	1	1	0	0
Bilirubin	6	0	0	0	0
Alkaline phosphatase	6	0	0	0	0
Haemoglobin	3	3	0	0	0
Leucocytes	2	1	1	1	1
Platelets	5	1	0	0	0
Pulmonary	2	3	0	0	1
Fever	4	2	0	0	0
Hair loss	4	2	0	0	0
Pain	0	4	2	0	0
Consciousness	5	1	0	0	0
Neurotoxicity	6	0	0	0	0
Chemoperitonitis	5	0	0	1	0

Side-effects (Tables 2, 3, 4). Grades 3 and 4 toxicity were observed only after 35–40 mg/m² mitoxantrone. There were 4 cases of leucopenia (Patients 1, 3, 10, 11—lowest nadir 800/mm³) and one case of chemoperitonitis (Patient 1). After dose regimens of up to 30 mg/m² there were only mild side-effects such as nausea and transient local pain (WHO grade 1, 2).

Clinical response. We observed 5 partial remissions (duration 2, 4+, 5, 5+, 8+ months) (see Table 5), 7 patients had stable disease (2, 3+, 4+, 4, 5+, 5, 6+ months) and 3 patients died within 2 months of entering the study. One patient had to be excluded because of infusion-related problems, 1 patient had

Table 4. Side-effects after i.p. mitoxantrone application

	44 cycles in 19 patients		
	No side-effects	Mild side-effects*	Severe side-effects†
≤ 20 mg/m²	9/11	2/11	0/11
25–30 mg/m²	10/27	17/27	0/27
35–40 mg/m²	0/6	2/6	4/6

*WHO grade 1 and 2: pain and nausea.
†WHO grade 3 and 4: leukopenia and chemoperitonitis.

Table 5. Partial remission in 5 patients with carcinomatosis peritonei

Patient	Age	Sex	Site of primary cancer	Duration of remission
3	56	F	Gastric	2 months
4	71	F	Ovary	5 months
11	47	F	Ovary	4+ months
18	46	F	Breast	5+ months
19	53	M	Mesothelioma	8+ months

a reduction of ascites (5 months) but had to be excluded because of appearance of extraperitoneal metastases, and with 2 patients treatment was discontinued because of progressive disease. Two patients were not evaluable for response because of the lack of measurable lesions. Further favourable clinical observations included 4 cases of disappearance of ascites, 6 cases of ascites reduction, 1 reduction of hydronephrosis and 4 cases with conversion of cytologic results from positive to negative.

Pharmacokinetic results

Peritoneal fluid, plasma and/or urine were analysed in 28 treatment cycles in 14 patients. The pharmacokinetic parameters are listed in Table 6. The peak concentrations in peritoneal fluid ranged from 282 to 56,800 ng/ml. The mean peritoneal clearance rate was 680 ml/min and resulted in a mean half-life of 13.1 h in the peritoneal space. The peak plasma concentration usually occurred 1–4 h after drug administration and ranged from 1 to 488 ng/ml. The mean urinary excretion in 12 patients (18 cycles) within 24 h was 0.42 ± 0.51% of the administered dose. In 4 patients the urinary excretion was measured between 24 and 48 h and accounted for 0.12 ± 0.11%. The mean ratio of AUC peritoneal fluid to plasma was 586. Pretreatment plasma concentrations in patients with prior treatment cycles were still high in some patients. In Patient 3, where the pretreatment value was 88 ng/ml, the course was complicated by marrow depression. Concentrations in plasma and peritoneal fluid showed great inter- and intrapatient variability.

DISCUSSION

Initial feasibility studies of i.p. chemotherapy in humans with 5-fluorouracil [3], doxorubicin [19], cisplatin [1], melphalan [20], cytarabine [21, 22] and mitomycin C [2] demonstrated the possibility of maintaining drug concentrations in the peritoneal cavity at levels 1–3 logs higher than in the plasma without severe local or systemic toxicity.

Our present pharmacokinetic data are in agreement with these results (Table 6): After i.p. administration of 20–40 mg/m² mitoxantrone a mean AUC value of 33 675 ng·h/ml was obtained in the peritoneal cavity, whereas the average AUC in the plasma was 2 log cycles lower (305 ng·h/ml), peak plasma mitoxantrone concentrations were in the range of 1–488 ng/ml. In contrast, we have previously reported that AUC values in the plasma were 1450 ng·h/ml and peak plasma concentrations were 400–1000 ng/ml after only 14 mg/m² when the drug was administered intravenously [23]. The lower systemic availability after i.p. administration is also reflected by a renal excretion of only 0.42% within 24 h after dosing, compared to 3.64% after i.v. administration [23]. These data demonstrate the pharmacokinetic advantage of the i.p. route of administration. The results also suggest that mitoxantrone is sequestered in the intraperitoneal tissue compartment and only slowly released. Four weeks after treatment plasma concentrations up to 88 ng/ml were measured, indicating that mitoxantrone is still released in an active form.

There was considerable inter- and intrapatient variability in our observations of pharmacokinetic parameters. A similar range was also reported by Alberts *et al.* [24]. The reasons for the wide variability in mitoxantrone concentrations are not clear, but may be attributed to differences in peritoneal cavity volume and/or compartmentalization of the cavity which could be responsible for at least part of the variability in i.p. concentrations. Furthermore, differences in peritoneal surface (through which the drug is absorbed into the systemic circulation) may give rise to different rates of absorption and could thus account for some of the variability in the plasma concentrations. In addition, factors such as patient status, peritoneal tumour burden and protein content and different drainage pathways of ascites may all contribute to the high range of values.

In the present study, mitoxantrone doses up to 30 mg/m² were well tolerated without appearance of grade 3 or 4 toxicity (WHO criteria [16]) and can safely be administered. In contrast, after 35–40 mg/m² grade 3 or 4 toxicity was observed in 4/6 treatment cycles. Also, abdominal pain occurred

Table 6. *Pharmacokinetic data*

Patient	Cycle	Dose (mg/m^2)	AUC (pf) (ng·h/ml)	AUC (p) (ng·h/ml)	AUC ratio (pf/p)	VD (l)	Half-life (h)	Clearance (ml/min)	Range (pf) (ng/ml)	Blank (p) (ng/ml)	Range (p) (ng/ml)	Conc.(max) ratio (pf/p)
1	IV	35		67						7.7	2.1–7.2	
1	V	40	25,570	288	88.8	26.5	7.9	39	800–2400	12.8	4.3–74.2	32.2
1	VI	40	8580	102	84.4	121.9	28.9	49	280–640	3.4	2.4–10.2	63.0
2	I	20	220	85	2.6	66.9	0.6	1808	13–304	0	13.2–30.0	10.1
3	II	25	60,140	833	72.2	8.9	14.5	7	1070–6510		16.0–59.0	110.3
3	III	30	45,178			11.7	7.1	19	530–5220			
3	IV	35	55,400	734	75.4	10.6	9.4	13	700–4500	88.0	12.8–128.0	35.2
3	V	20	29,860	410	72.8	9.8	6.5	17	420–3200	34.7	7.4–64.0	50.0
4	I	20	5474	60	90.8	98.9	27.7	41	112–586		17.0–23.5	24.9
5	I	20	506			106.1	9.8	125	75–650	0	1.0	650.0
6	I	20	5171	104	49.6	61.0	6.9	102	54–717	0	23.9–34.2	21.0
6	II	25	16,315	293	55.6	36.7	21.4	20	250–1460	5.3	5.9–37.3	39.1
6	III	30	75,970	901	84.3				1280–4400		29.3–80.0	55.0
9	I	20	2140			161.3	15.5	120	64–380	0	1.0–3.4	111.4
9	II	25	1239			144.0	8.4	197	102–420	0	3.9	107.7
10	I	20	17,984	256	70.3	19.7	4.8	47	64–2560		8.0–25.3	101.2
15	I	30	2396	8	284.6				30–282	0	1.8–3.2	89.2
16	I	30	7226	79	92.0				151–570	0	2.5–30.9	18.4
17	I	30	94,000	6	15,692.8	849.0	1.0	9617	103–56,800	0	2.8–4.4	12,909.1
18	I	20	84,489	519	162.8	5.8	14.6	5	2670–7000	0	11.7–41.6	168.3
18	II	20	128,039	378	330.9	4.3	22.2	2	4270–8960	2.0	16.8–488	18.4
18	III	20	22,976	240	95.7				422–1540	1.0	1.8–22.9	67.2
18	IV	20	39,091	173	225.6				300–2840	0	2.1–21.7	130.9
19	I	30	11,619	222	52.5				173–1260	0	2.0–55.6	22.7
19	II	30	7130	380	18.8				26–417	2.6	3.1–93.3	4.5
19	III	40	10.639	612	17.4				72–1373	0	6.0–100.9	13.6
19	IV	40	12,300	536	22.9				18–810	0	8.3–72.4	11.2
21	I	20	139,569	18	7753.8	13.3	28.6	5	170–4170	0	2.3–11.0	379.1
Mean			33,675	305	1108.5	97.6	13.1	680				586.3
S.D.			38,761	260	3479.6	189.1	8.9	2205				2468.2

AUC: Area under curve, VD: volume of distribution, p: plasma, pf: peritoneal fluid.

after only 6/38 treatments with the lower doses, as compared to 6/6 after the high doses. Pain relief could always be achieved by systemic analgesic therapy. These observations suggest setting the maximal i.p. dose at 30 mg/m^2.

Histological diagnoses and patient status were heterogeneous. Partial remissions were observed in 5 out of 14 patients so far evaluable. Further therapeutic effects were noticed in 7 patients, namely disappearance or reduction of ascites. Compared with other drugs used for i.p. treatment, for example cisplatin [15], mitoxantrone seems to have a comparable response rate with less systemic and local side-effects at the recommended dosage of 30 mg/m^2.

In conclusion, the efficacy, low grade toxicity and the demonstrated pharmacokinetic advantage of i.p. administration warrant phase II studies using the recommended dose of 30 mg/m^2 i.p. every 3–4 weeks.

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