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Pharmacokinetics of intraperitoneal hyperthermic perfusion with mitoxantrone in ovarian cancer

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Abstract *Purpose*: Theoretical data and experimental assumptions indicate that intraperitoneal hyperthermic chemotherapy may play a role in the treatment of peritoneal carcinomatosis. The feasibility, tolerability and pharmacokinetics of intraperitoneal hyperthermic perfusion with mitoxantrone were studied in patients with pretreated ovarian cancer. *Methods*: After cytoreductive surgery, 11 patients underwent intraperitoneal hyperthermic perfusion with mitoxantrone. A heated (42–43 °C) solution of the drug (28 mg/m^2) was recycled through a perfusion apparatus into the abdominal cavity for 90 min. Treatment was repeated every month for two to four cycles. In six patients blood and peritoneal perfusate samples were collected at 0.5, 1, 1.5, 2, 4, 8, 16 and 24 h after drug administration and mitoxantrone was assayed by an HPLC method. *Results*: Although treatment was generally well tolerated, all patients developed transient intestinal subocclusion. Maximal mitoxantrone plasma concentrations (C_{max}), times to C_{max} (T_{peak}) and area under the curves (AUC) were highly variable between subjects (C_{max} 14–337 ng/ml; T_{peak} 0.5–8 h; AUC 222–4130 ng · ml^{-1} · h). The plasma to peritoneal fluid AUC ratio was significantly higher during the second (0.177) than during the first cycle (0.066), suggesting a cycle-dependent increase in systemic bioavailability. Furthermore, when comparing present data with those reported previously, hyperthermic perfusion may have lowered the mitoxantrone levels in the peritoneal fluid without greatly influencing plasma levels. *Conclusions*: Intraperitoneal mitoxantrone administered under hyperthermia to advanced ovarian cancer patients is feasible and well tolerated. Mitoxantrone pharmacokinetics may be altered by repeated intraperitoneal administration (increased bioavailability) and by hyperthermic perfusion (possibly, increased peritoneal tissue uptake).

Key words Mitoxantrone · Ovarian cancer · IPHP · Pharmacokinetics · Hyperthermia

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Introduction

Considerable effort has been devoted in recent years to improving the therapeutic outcome of ovarian cancer. While cytoreductive surgery followed by platinum/paclitaxel therapy is currently considered the standard [27], several other drugs and drug combinations have been tested (especially in tumour relapses and/or resistance) [1] and new delivery modalities have been explored. One of the most promising approaches has proved to be intraperitoneal (i.p.) drug administration [20, 23], which is based on the fact that ovarian cancer tends to remain confined to the abdominal cavity and on the assumption that local exposure to high chemotherapeutic agent concentrations increase the tumour cytotoxic effect without increasing systemic toxicity. A large-scale

clinical trial has recently demonstrated that the cisplatin-cyclophosphamide combination gives a better clinical response and lower toxicity when cisplatin is given by the i.p. as compared with the intravenous route [3].

It is also well recognized that hyperthermia, besides having its own antineoplastic effect, may increase the cytotoxic potential of anticancer drugs by increasing cell membrane permeability and drug transport [13, 16]. These findings encouraged infusion of cytotoxic drugs into the peritoneal space at supraphysiologic temperatures (i.p. hyperthermic perfusion, IPHP) [6, 29]. So far, only platinum compounds have been administered by IPHP to treat patients with advanced ovarian cancer [10, 15, 17, 30]. The aim of the present study was to evaluate the feasibility, tolerability and pharmacokinetics of i.p. administration of mitoxantrone under hyperthermic conditions. Previous work had suggested that this anthracenedione compound, given by the standard i.p. route, produces favourable clinical responses in advanced, pretreated ovarian cancer [2, 4, 5, 21, 25, 26].

Patients and methods

Patient characteristics

The study protocol was approved by the Hospital Ethical Committee. Between October 1994 and January 1996, 11 pretreated patients were enrolled in the study after having given their written informed consent. Eligibility criteria included histologically confirmed ovarian carcinoma, life expectancy of at least 3 months, WHO performance status <3 [31], normal hepatic function (normal total bilirubin, AST not more than 1.5 times the upper limit of normal, alkaline phosphatase less than five times the upper limit of normal) and kidney function (creatinine concentration <2.0 mg/dl). Patients also had to have adequate bone marrow function (absolute neutrophil count >1500 cells/μl, platelet count $>100{,}000$ cells/μl) and no clinical evidence of cardiac disease (assessed by ECG and arterial pressure). The stage of disease was established according to the FIGO classification [9]. All patients in this trial had been treated 1 to 6 months before IPHP with polychemotherapy including platinum, anthracyclines and alkylating agents.

Intraperitoneal hyperthermic perfusion

All patients had previously undergone primary cytoreductive surgery for curative purposes. Three of them had undergone secondary cytoreduction at the time of second-look laparotomy. In these cases, the first IPHP cycle was carried out at the end of the surgical procedure before closure of the abdominal wall. In the other cases and in all the subsequent cycles IPHP was performed by peritoneal catheterization under light sedation. The procedure was similar to that originally described by Fujimoto et al. [11]. Two catheters (Peritofix-Brown) were inserted into the peritoneal space with a Veress needle, one positioned in the epigastric area (entry line) and the other in the Douglas pouch (exit line). They were connected to a perfusion apparatus consisting of a peristaltic pump (Therathermic, Vigevano, Italy) filled with saline solution and a heat exchanger. A filtering system capable of trapping peritoneal fluid cells was inserted in the exit line. Saline solution was gradually warmed to 44 °C and infused at a flow rate of 250 ml/min keeping the drain cock closed until an intraperitoneal volume of 2000 ml had been attained. During solution recycling, the outflow temperature ($\pm$SEM) was 42.3 $\pm$ 0.26 °C on average, while the body temperature was continuously monitored and kept within physiologic limits. Once the washing solution had been completely filtered and the temperature stabilized, mitoxantrone (28 mg/m^2) was added to the saline and recycled for 90 min. Treatment was terminated by allowing the peritoneal fluid to drip out by gravity.

Although evaluation of response to therapy was not the aim of our study, objective changes in tumour size were measured by CT scan, echotomography or laparoscopy (in one case), according to standard criteria [31]. In the case of a favourable outcome, the duration of response was also calculated.

Toxicity

Haematological, cardiac, renal, local and gastrointestinal toxicities were evaluated according to WHO criteria [31].

Pharmacokinetic study

Blood samples for drug assay were collected during the first cycle of treatment and then during the second, 1 month later. Sampling times after mitoxantrone addition to IPHP were: 0.5, 1, 1.5, 2, 4, 8, 16 and 24 h. Blood was centrifuged at 3500 rpm and plasma frozen at −7 °C until analysed. Peritoneal fluid samples were taken at the same times and stored in the same way. Drug concentrations were determined by means of a previously described HPLC method [25]. The lowest detection limit was 2 ng/ml. Within-day and between-day variabilities, measured at 50 ng/ml, were 5.2% and 8.4%, respectively. Drug stability at the perfusion temperature was preliminarily tested by assaying drug concentration in a saline solution kept at 45 °C for 4 h. The area under the concentration vs time curve from 0 to 24 h (AUC_{0-24}) was calculated in plasma and peritoneal fluid by the trapezoidal rule. Maximal concentration (C_{max}) and time to C_{max} (T_{peak}) were also recorded. The ratio between the AUCs in plasma and peritoneal fluid (AUC_{PL}/AUC_{PE}) was calculated and adopted as an index of systemic drug bioavailability. Data are presented as means $\pm$ SEM. Comparisons between the pharmacokinetic parameters obtained during the first and the second treatment cycle were carried out by Student's two-tailed paired *t*-test.

Results

Therapeutic results

The characteristics of individual patients and clinical outcomes are shown in Table 1. All patients had been previously treated with polychemotherapy (including platinum compounds, anthracyclines and alkylating agents) and all but one had macroscopic residual disease (<5 mm in seven; >5 mm in four).

IPHP was repeated every month for two to four cycles, except in two patients who received only one treatment. In no case did the initial mitoxantrone dose (28 mg/m^2) have to be reduced because of severe toxicity. No patient complained of abdominal pain or had haematological, cardiac or infective complications. However, all developed transient, self-resolving intestinal subocclusion.

Of ten patients with residual disease one (no. 5) was evaluated by laparoscopy and had a complete response which lasted 15 months. The others were evaluated by CT scan or echotomography and their clinical outcome was as follows: two (nos. 2 and 7) had no evidence of disease for 2 months and then relapsed, two (nos. 8 and

Table 1 Patient characteristics (*E* endometrioid, *M* mucinous, *SP* serous-papillary; *ND* not determined; *A* Adriamycin, *C* cyclophosphamide, *F* 5-fluorouracil, *M* mitoxantrone, *P* platinum compounds)

Patient	Age (years)	Stage	Histopathology	Grade	Residuum	Number of IPHP cycles	Previous treatment	Present condition[a]
1	38	1B	E	2	Absent	2	P + A + C	Alive
2	55	3C	SP	2	< 5 mm	2	P + C	Deceased
3	55	3C	SP	2	< 5 mm	1	P + C	Deceased
4	63	3B	M	3	< 5 mm	3	P + C	Deceased
5	61	3C	SP	3	< 5 mm	3	P + C; F + P	Alive
6	64	3C	SP	2	< 5 mm	3	P + C; F + P	Deceased
7	74	3A	SP	1	< 5 mm	2	P + C	Deceased
8	31	3B	SP	2	< 2 cm	2	M + P; F + P	Deceased
9	68	3C	SP	2	> 2 cm	2	M + P; F + P	Deceased
10	52	3C	SP	2	< 5 mm	4	P + C; F + P	Alive
11	39	3B	E	ND	< 2 cm	1	P + C	Deceased

[a] At the time of writing (July 1999)

9) showed no change in tumour size, and five (nos. 3, 4, 6, 10 and 11) showed disease progression. Patient no. 1, who had no residual disease after surgery and underwent consolidation treatment, was still alive and disease-free at the time of writing (July 1999).

Pharmacokinetic data

It was possible to carry out a pharmacokinetic study in six patients during the first cycle and repeated in five patients during the second. All parameters measured (C_{max}, T_{peak}, AUC_{0-24}, AUC_{PL}/AUC_{PE}) showed great interpatient variability (Table 2). In addition, in cases in which two separate measurements were available, plasma C_{max}, plasma AUC_{0-24} and AUC_{PL}/AUC_{PE} were significantly higher during the second cycle than during the first (C_{max} 160 ± 46 vs 66 ± 41 ng/ml, $P = 0.0009$; AUC_{0-24} 2353 ± 505 vs 827 ± 409 ng/ml · h, $P = 0.0022$; AUC_{PL}/AUC_{PE} 0.177 ± 0.043 vs 0.066 ± 0.033, $P = 0.0125$). Also, the mean AUC_{0-24} in peritoneal fluid was slightly but significantly higher in the second cycle (17,230 ± 3235 vs 15,860 ± 3000 ng/ml · h, $P = 0.044$). In contrast, T_{peak} in both plasma and peritoneal fluid did not differ between the two cycles.

The mean time-courses of mitoxantrone concentrations in plasma and peritoneal fluid measured during the first and second cycles are shown in Fig. 1. It can be appreciated that, after drug removal from the peritoneal cavity: (1) drug concentrations sharply decreased in peritoneal fluid but not in plasma, indicating that peritoneal and plasma compartments are not in fast equilibrium; (2) mean concentrations were constantly higher in peritoneal fluid than in plasma, suggesting the operation of an intraperitoneal trapping mechanism; (3) from the 8th hour onwards, drug concentrations in the two matrices declined roughly in parallel; (4) there was no apparent difference in plasma concentration decline rate the first and second cycle.

Given the small number of patients and the great pharmacokinetic intersubject variability, no attempt was made to correlate mitoxantrone plasma levels with clinical outcome.

Discussion

To our knowledge, no studies on mitoxantrone IPHP in advanced ovarian cancer have so far been published. At present, evidence for possible IPHP effectiveness in ovarian cancer has been provided for platinum compounds. In vitro experiments [21] on cisplatin-sensitive and cisplatin-resistant human ovarian carcinoma cells have shown that hyperthermia enhances cisplatin effectiveness, especially in the drug-resistant cell line. The same research group [30] have demonstrated that, following cisplatin IPHP treatment in ovarian cancer patients, cisplatin-DNA adduct formation is higher in tumour cells than in buccal cells, suggesting an increased effect of the local drug application combined with hyperthermia. In two other clinical studies [10, 17], favourable clinical responses in patients with minimal residual disease in terms of both patient survival and CA-125 count decrease have been found. Clinical effectiveness of IPHP combined with chemotherapy has also been documented for other antineoplastic drugs (mitomycin C) and other forms of disseminated peritoneal carcinomatosis (gastrointestinal and colorectal tumours) [8, 11, 12, 14, 18, 28].

Our phase I-II study indicates that IPHP with mitoxantrone (28 mg/m^2) in patients with advanced pretreated ovarian cancer is feasible and well tolerated. Apart from the frequent occurrence of temporary intestinal transit disturbances, the incidence of side effects was unusually low. At variance with other reports, no patient complained of abdominal pain during the IPHP procedure. Clearly, the study design and population size do not allow us to draw any conclusions about the therapeutic effectiveness of mitoxantrone hyperthermic perfusion. Three out of ten patients with residual disease exhibited clinical responses, and one patient without residual disease was still disease-free 48 months after IPHP treatment. The response rate previously reported in the same type of patients following standard i.p. mitoxantrone administration is about 30% [21, 25].

With regard to pharmacokinetics, great inter- and intrapatient variabilities in both plasma and peritoneal

Table 2 Pharmacokinetic parameters

Patient no.	First cycle							Second cycle						
	Plasma			Peritoneal fluid			AUC_{PL}/AUC_{PE}	Plasma			Peritoneal fluid			AUC_{PL}/AUC_{PE}
	C_{max} (ng/ml)	T_{peak} (h)	AUC (ng/ml · h)	C_{max} (ng/ml)	T_{peak} (h)	AUC (ng/ml · h)		C_{max} (ng/ml)	T_{peak} (h)	AUC (ng/ml · h)	C_{max} (ng/ml)	T_{peak} (h)	AUC (ng/ml · h)	
1	27	4	389	3500	0.5	20,270	0.036	133	4	1833	4000	0.5	20,720	0.172
2	35	0.5	614	2200	0.5	8293	0.074	143	0.5	2438	2900	0.5	8820	0.276
5	228	1	2444	3500	0.5	12,840	0.190	337	1	4130	4750	0.5	15,220	0.271
6	24	8	467	6700	0.5	12,840	0.019	118	8	2304	6900	0.5	13,370	0.088
7	14	1	222	8400	0.5	25,080	0.009	68	1	1062	6900	0.5	13,670	0.078
11	130	0.5	2081	6300	0.5	13,880	0.150	–	–	–	–	–	–	–
Mean	76	–	1036	5100	–	15,530	0.080	160	–	2353	4860	–	17,230	0.177
SEM	35	–	394	973	–	2471	0.030	46	–	505	1155	–	3235	0.043

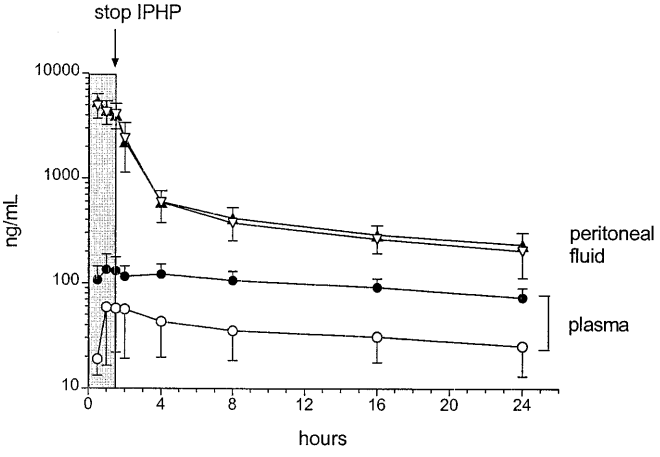

Fig. 1 Time courses of mean (±SEM) mitoxantrone concentrations in plasma (*circles*) and peritoneal fluid (*triangles*) during the first cycle (*open symbols*) and the second cycle (*filled symbols*)

fluid parameters (AUC_{0-24}, C_{max}, T_{peak}, AUC_{PL}/AUC_{PE}) were apparent. This finding is in agreement with all previous reports on mitoxantrone pharmacokinetics after conventional i.p. administration. However, an additional variability factor associated with IPHP may be incomplete drug distribution into the peritoneal space due to possible formation of preferential flow channels in the abdominal cavity, which may limit, in turn, the speed and completeness of drug absorption.

Interestingly, while the C_{max} and AUC values in plasma were within the range previously reported following comparable i.p. doses [7, 14, 24, 25], the AUC_{PL}/AUC_{PE} ratio was about 100 times higher (about 0.1 vs about 0.001; see references 2, 4 and 7). Although a formal statistical comparison with other studies cannot be carried out, this observation suggests that IPHP may lower mitoxantrone levels in peritoneal fluid without inducing major changes in plasma levels.

This behaviour is not easy to explain according to conventional absorption models, but some findings from the present study and others may be considered. It has been shown that mitoxantrone is extensively bound to peritoneal tissues and that binding persists for months after drug withdrawal [22]. Moreover, since drug removal from the peritoneal space does not appreciably affect plasma concentration decay (our results; [24]), plasma and peritoneal mitoxantrone concentrations must be in very slow kinetic equilibrium. It may therefore be hypothesized that peritoneal tissue serves as a kind of deep "buffer" compartment, which accommodates mitoxantrone during absorption and releases it after withdrawal. This model may partly explain the great AUC_{PL}/AUC_{PE} ratio variability (different peritoneal uptake) and explain why, after drug withdrawal, mitoxantrone concentrations in peritoneal fluid remained higher than in plasma (continuous drug release into a limited space). It is conceivable that, under our experimental conditions, hyperthermia decreased the AUC_{PL}/AUC_{PE} ratio by increasing the binding capacity

of peritoneal tissues. This hypothesis is in agreement with the experimental data reported by Los et al. [19], who found that, in rats bearing peritoneal tumours, regional hyperthermia increases cisplatin uptake not only into tumour cells (by a factor of 4.1) but also into normal tissues, such as the kidney, liver, spleen and lung (by a factor of about 2).

We also found that plasma AUC_{0-24} and AUC_{PL}/AUC_{PE} consistently increased from the first to the second treatment cycle (from 0.065 to 0.177, on average). A similar phenomenon has been observed by Nagel et al. [24], who found that the more often patients had received i.p. mitoxantrone previously, the greater was their peritoneal drug removal. According to our hypothesis, this cycle-dependent kinetics may be explained by saturation of the buffering capacity of the peritoneum, which in turn allows a greater amount of mitoxantrone to escape tissue uptake and pass into the circulation. Alternatively, saturation or reduction in liver enzyme activity may have occurred after the first cycle with a consequent decrease in first-pass liver drug inactivation and increase in systemic bioavailability. If this were the case, drug elimination should have been slowed as well. However, our finding of similar plasma concentration decay rates during the first and the second cycles (Fig. 1) argues against an impairment in liver elimination capacity.

The observation of an increased plasma AUC during the second cycle is not merely of academic interest since, according to our previous results [25], the clinical outcome in ovarian cancer is significantly better when local i.p. administration produces higher systemic mitoxantrone plasma levels. Thus, a synergism may exist between the fraction of drug absorbed directly from the peritoneal surface and that reaching the deeper tumour layers through the systemic circulation. Therefore, factors changing both plasma and peritoneal fluid mitoxantrone concentrations may affect the clinical response.

In conclusion, this study shows that i.p. mitoxantrone administered under hyperthermia to advanced ovarian cancer patients can induce a response in about 30% of cases and that it is well tolerated. Further work is needed to ascertain whether this approach is superior to standard i.p. administration and whether it can also be applied in earlier cancer stages. Analysis of pharmacokinetic data suggests that peritoneal and plasma drug disposition may be affected by IPHP and previous therapy cycles.

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References

1. Alberts DS (1999) Treatment of refractory and recurrent ovarian cancer. Semin Oncol 26 [Suppl I]: 8
2. Alberts DS, Surwit EA, Peng YM, et al. (1988) Phase I clinical and pharmacokinetic study of mitoxantrone given to patients by intraperitoneal administration. Cancer Res 48: 5874
3. Alberts DS, Liu PY, Hanningan EV, et al. (1996) Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med 335: 1950
4. Blochl-Daum B, Eichler HG, Rainer H, et al. (1988) Escalating dose regimen of intraperitoneal mitoxantrone: phase I study – clinical and pharmacokinetic evaluation. Eur J Cancer Clin Oncol 24: 1133
5. Dufour P, Bergerat JP, Barats JC, et al. (1994) Intraperitoneal mitoxantrone as consolidation treatment for patients with ovarian carcinoma in pathologic complete remission. Cancer 73: 1865
6. Elias D, Detroz B, Debaene B, et al. (1994) Treatment of peritoneal carcinomatosis by intraperitoneal chemo-hyperthermia: reliable and unreliable concepts. Hepatogastroenterology 41: 207
7. Faulds D, Balfour JA, Chrisp P, Langtry HD (1991) Mitoxantrone. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in the chemotherapy of cancer. Drugs 41: 400
8. Fernandez-Trigo V, Stuart OA, Stephens AS, Hoover LD, Sugarbaker PH (1996) Surgically directed chemotherapy: heated intraperitoneal lavage with mitomycin C. Cancer Treat Res 81: 51
9. FIGO Cancer Committee (1986) Staging announcement. Gynecol Oncol 25: 383
10. Formenti SC, Shrivastava PN, Saponzik M, et al. (1996) Abdomino-pelvic hyperthermia and intraperitoneal carboplatin in epithelial ovarian cancer: feasibility, tolerance and pharmacology. Int J Radiat Oncol Biol Phys 35: 993
11. Fujimoto S, Takahashi M, Mutou T, et al. (1997) Improved mortality rate of gastric carcinoma patients with peritoneal carcinomatosis treated with intraperitoneal hyperthermic chemoperfusion combined with surgery. Cancer 79: 884
12. Gilly FN, Carry PY, Sayag AC, et al. (1994) Regional chemotherapy (with mitomycin C) and intraoperative hyperthermia for digestive cancers with peritoneal carcinomatosis. Hepatogastroenterology 41: 124
13. Hahn GM (1979) Potential for therapy of drugs and hyperthermia. Cancer Res 39: 2264
14. Jacquet P, Averbach A, Stephens AD, Stuart OA, Chang D, Sugarbaker PH (1998) Heated intraoperative intraperitoneal mitomycin C and early postoperative intraperitoneal 5-fluorouracil: pharmacokinetic studies. Oncology 55: 130
15. Kober F, Heiss A, Roka R (1996) Diffuse and gross peritoneal carcinomatosis treated by intraperitoneal hyperthermic chemoperfusion. Cancer Treat Res 82: 211
16. Kowal CD, Bertino JR (1979) Possible benefits of hyperthermia to chemotherapy. Cancer Res 39: 2285
17. Leopold KA, Oleson JR, Clarke-Pearson D, et al. (1993) Intraperitoneal cisplatin and regional hyperthermia for ovarian carcinoma. Int J Radiat Oncol Biol Phys 27: 1245
18. Loggie BW, Perini M, Fleming RA, Russel GB, Geisinger K (1997) Treatment and prevention of malignant ascites associated with disseminated intraperitoneal malignancies by aggressive combined-modalities therapy. Am Surg 63: 137
19. Los G, Sminia P, Wondergem J, et al. (1991) Optimization of intraperitoneal cisplatin therapy with regional hyperthermia in rats. Eur J Cancer 27: 472
20. Markman M (1996) Intraperitoneal chemotherapy in the treatment of ovarian cancer. Ann Med 28: 293
21. Markman M, George M, Hakcs T, et al. (1990) Phase II trial of intraperitoneal mitoxantrone in the management of refractory ovarian cancer. J Clin Oncol 8: 146
22. Markman M, Alberts D, Rubin S, et al. (1993) Evidence for persistence of mitoxantrone within the peritoneal cavity following intraperitoneal delivery. Gynecol Oncol 48: 185
23. Markman M, Reichman B, Hakes T, et al. (1993) Intraperitoneal chemotherapy in the management of ovarian cancer. 71 [Suppl 4]: 1565
24. Nagel JD, Varossieau FJ, Dubbelman R, Bokkel Huinink WW ten, McVie JG (1991) Clinical pharmacokinetics of mitoxant-

rone after intraperitoneal administration. Cancer Chemother Pharmacol 29: 480
25. Nicoletto MO, Padrini R, Ferrazzi E, et al. (1993) Phase-II intraperitoneal mitoxantrone in advanced pretreated ovarian cancer. Eur J Cancer 29A: 1242
26. Oza AM, Bokkel Huinink W ten, Dubbelman R, et al. (1994) Phase I/II study of intraperitoneal mitoxantrone in refractory ovarian cancer. Ann Oncol 5: 343
27. Schink JC (1999) Current initial therapy of stage III and IV ovarian cancer: challenges for managed care. Semin Oncol 26 [Suppl I]: 2
28. Schneebaum S, Arnold MW, Staubus A, Young DC, Dumond D, Martin EW Jr (1996) Intraperitoneal hyperthermic perfusion with mitomycin C for colorectal cancer with peritoneal metastases. Ann Surg Oncol 3: 44
29. Spratt JS, Adcock RA, Muskovin M, Sherrill W, McKeown J (1980) Clinical delivery system for intraperitoneal hyperthermic chemotherapy. Cancer Res 40: 256
30. Van de Vaart PJ, Vange N van der, Zoetmulder FA, et al. (1998) Intraperitoneal cisplatin with regional hyperthermia in advanced ovarian cancer: pharmacokinetics and cisplatin-adduct formation in patients and ovarian cancer cell lines. Eur J Cancer 34: 148
31. World Health Organization (1979) Handbook for reporting results of cancer treatment (Offset Publication No. 48). WHO, Geneva