Pharmacokinetic study of docetaxel in intraoperative hyperthermic i.p. chemotherapy for ovarian cancer

Eelco de Bree[a], Hilde Rosing[b], Jos H. Beijnen[b], John Romanos[a], John Michalakis[a], Vasilis Georgoulias[c] and Dimitris D. Tsiftsis[a]

The purpose of this study was to evaluate the pharmacokinetics and toxicity of docetaxel in continuous hyperthermic perfusion peritoneal chemotherapy (CHPPC) after cytoreductive surgery for peritoneal involvement of gynecological malignancies, mainly ovarian cancer. Eighteen patients, with a mean age of 64 years (range 51–80), underwent cytoreductive surgery and subsequent CHPPC with 75 mg/m^2 docetaxel at 41–43°C. One patient was treated twice. In eight cases, peritoneal fluid and blood samples were obtained for pharmacokinetic analysis. Death occurred in two heavily pretreated elderly patients with a high volume i.p. tumor recurrence, probably reflecting poor patient selection (mortality rate 10.5%). Other complications, mainly minor, were recorded after 63% of the procedures. Hematological docetaxel-induced toxicity was limited, while the incidence of wound complications was relatively high and probably caused by the direct exposure of the wound to docetaxel during CHPPC. The maximal i.p. versus plasma concentration ratio ranged from 17 to 95 (average 45), while the i.p. versus systemic exposure ratio varied between 105 and 555 (average 207). We conclude that the use of docetaxel in CHPPC following cytoreductive surgery seems feasible and results in a high i.p. versus systemic exposure ratio. The AUC for the peritoneal cavity is on average 13–27 times higher after i.p. administration of 75 mg/m^2 during CHPPC than the AUC achieved in the systemic compartment after i.v. administration of the recommended dose of 100 mg/m^2, while docetaxel-induced systemic toxicity is highly limited. *Anti-Cancer Drugs* 14:103–110 © 2003 Lippincott Williams & Wilkins.

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Departments of [a]Surgical Oncology, [c]Medical Oncology, University Hospital, Herakleion, Greece and [b]Department of Pharmacy and Pharmacology, Slotervaart Hospital/The Netherlands Cancer Institute, Amsterdam, The Netherlands.

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Correspondence to E. de Bree, Department of Surgical Oncology, University Hospital, P.O. Box 1352, 71 110 Herakleion, Greece.
Tel: +30 2810 542096; fax: +30 2810 542059;
e-mail: debree@edu.uoc.gr

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Introduction

Despite the high response rate of patients with advanced ovarian cancer following primary cytoreductive surgery and platinum–paclitaxel systemic combination chemotherapy, the tumor ultimately recurs and the 5-year survival rate remains about 20% [1]. Future directions for the management of ovarian cancer to improve survival include new regimens with novel drugs and different timing, high-dose i.v. chemotherapy, i.p. drug delivery and other experimental modalities [2]. Dose intensification may overcome the problem of relative drug resistance of the tumor [3,4]. Because ovarian cancer remains largely confined to the peritoneal cavity, i.p. delivery of a variety of cytotoxic agents has been investigated in an attempt to increase drug exposure and dose intensity in the absence of systemic toxicity [5,6]. Recently, two large randomized trials demonstrated 8–9 months overall survival benefit and an increased recurrence-free survival for patients with minimal residual stage III ovarian cancer, when treated by i.p. chemotherapy with cisplatin in comparison with those treated by only systemic chemotherapy following cytoreductive surgery as first-line treatment [7,8]. Several phase II studies of second-line i.p. chemotherapy in recurrent ovarian cancer reported a moderate survival improvement [4]. However, a major observation from early i.p. chemotherapy trials was that ovarian cancer patients who failed to respond to prior systemic chemotherapy did not respond to i.p. platinum, suggesting that i.p. delivery of platinum was unlikely to reverse a clinically platinum-resistant disease to a platinum-sensitive one [9]. Therefore, other drugs should be used in platinum-resistant tumors to improve survival.

Taxanes have shown considerable activity against ovarian cancer and lack cross-resistance with platinum compounds. Paclitaxel is currently the most commonly used taxane, although docetaxel seems to be at least equally effective in systemic chemotherapy for primary or recurrent advanced epithelial ovarian cancer [1,10–12]. *In vitro* docetaxel seems to be even more potent in

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different cell lines and investigational models than paclitaxel [12]. Since the majority of patients are currently treated with a platinum–paclitaxel combination as first-line chemotherapy, it is of major importance that no cross-resistance exists. Docetaxel may be active not only in platinum-resistant but also in paclitaxel-resistant gynecological and breast malignancies [13,14]. Comparisons of various studies support a dose–response relationship for taxanes in platinum-resistant recurrent ovarian cancer [15]. Because taxanes have a high molecular weight, non-vesicant properties and hepatic metabolism, a high i.p. to systemic drug exposure ratio might be achieved after i.p. delivery. Intraperitoneal administration of paclitaxel has been demonstrated to be tolerable until a dose of 125 mg/m^2 and active in patients with residual ovarian cancer [16–19], whereas, as far as we know, docetaxel has never been delivered i.p. in humans. Recently, favorable pharmacokinetics and tissue distribution were demonstrated after i.p. administration of docetaxel in a rat model [20].

Hyperthermia may enhance drug efficacy and penetration depth, while it has also a direct cytotoxic effect [21]. During the last decade, continuous hyperthermic intracavitary perfusion chemotherapy following cytoreductive surgery has been used for malignant peritoneal and pleural mesothelioma, pseudomyxoma peritonei, and peritoneal dissemination of colorectal and gastric carcinoma with promising results, regarding both overall and disease-free survival, and control of malignant effusion [22–26]. The experience with this treatment modality in patients with peritoneal dissemination from ovarian cancer is, however, still limited [27–34].

Since 1995, participants of our multi-disciplinary team have been involved in the use of the latter treatment modality for various primary and secondary peritoneal and pleural malignancies [22–24,33–40]. Herein, we report the pharmacokinetic analysis of docetaxel in intraoperative continuous hyperthermic peritoneal perfusion chemotherapy (CHPPC) following cytoreductive surgery in patients with peritoneal involvement of ovarian or uterine malignancies.

Patient and methods

Patient eligibility

Patients with peritoneal carcinomatosis of gynecological malignancies and absence of evidence of extra-abdominal and parenchymal metastases were treated by cytoreductive surgery and CHPPC with docetaxel. All patients were previously operated for their histologically confirmed malignancy. The patient's WHO performance status had to be ≤ 2. Blood cell count and biochemical liver and renal function tests had to be within the normal range. The protocol was approved by the local ethics committee and informed consent was obtained from all patients.

Cytoreductive surgery and i.p. chemotherapy

The technique of cytoreductive surgery and CHPPC used in our institution has been previously described in detail elsewhere [38]. In short, the abdomen is approached through a median xyphoid-pubic incision. Comprehensive adhesiolysis is performed. The primary tumor is excised, if still present, and all visceral or parietal peritoneal surface tumor deposits are removed as completely as possible. If a deposit is infiltrating deeply into an organ and it is impossible to peel the malignancy from its surface, the involved organ or a segment of it is excised. The objective of cytoreductive surgery is to leave no macroscopic disease or, when this is impossible, tumor deposits of less than 0.5 cm in diameter behind. Subsequently, after closing the skin of the laparotomy wound only and placement of in- and outflow catheters, the peritoneal cavity is perfused using a closed perfusion model with a roller pump and a heat exchanger. The system is filled with 4–9 l of normal saline, in most cases approximately 3.5 l/m^2 body surface area, resulting in a mean intra-abdominal pressure of 12–26 mmHg. The pump system is started and the circulating perfusate is heated. When the i.p. temperature reaches 41°C, a dose of 75 mg/m^2 docetaxel dissolved in polysorbate 80 and subsequently diluted in its solvent of 13% w/w ethanol in water (Taxotere; Aventis Pharma, Antony Cedex, France) is administered. The i.p. temperature is allowed to fluctuate between 41 and 43°C, and the duration of the perfusion is 2 h. To facilitate uniform temperature and drug distribution throughout the peritoneal cavity vigorous agitation of the abdomen is performed continuously. The core temperature is kept below 38.5°C. After completion of the CHPPC the abdomen is reopened, and the canulae, temperature and pressure probes are removed. The excess fluid is drained from the abdominal cavity, but no attempt is made to dry the abdominal cavity. One drain in Douglas' pouch is left in place for postoperative drainage. The abdominal wall is closed in layers in the usual way. Perioperatively, dexamethasone and antihistamines were administered i.v. to minimize the chance on docetaxel-induced hypersensitivity reactions and to delay the onset of docetaxel-induced fluid retention as recommended in different studies [10,41].

Pharmacokinetic study

From eight patients blood and perfusate samples were obtained for measurement of docetaxel levels. Blood samples were collected during and after CHPPC at 0.5, 1, 1.5, 2, 2.5 and 3 h after administration of docetaxel. Subsequently blood samples were obtained at 3-h intervals until 24 h after drug administration, at 6-h intervals during the following 2 days and at 12-h intervals

during the last 2 days. The last of the 27 blood samples was collected 5 days after docetaxel administration. During CHPPC perfusate samples were obtained just after docetaxel administration (at 5 min) and at the end of the perfusion (at 2 h). After 5 min the drug was considered to be equivocally distributed in the perfusate and the sample at this moment represents the maximal drug concentration in the perfusate. Postoperatively, peritoneal fluid samples were obtained from the abdominal drain which was left in place in Douglas' pouch 24 h after the start of the CHPPC and each consecutive day, until the drain was removed or postoperative day 5 was reached. After withdrawal, the samples were immediately centrifuged (10 min at 2500 *g*), and the plasma layer was removed and stored at –30°C. After completion of entry of patients in this study, drug concentrations were determined by means of a semi-automated reversed-phase HPLC method, which has been described previously in detail [42]. The lower limit of quantification was 10 ng/ml. The area under the concentration–time curve (AUC) was calculated by the trapezoidal rule in peritoneal fluid and in plasma. For peritoneal fluid the time interval was from 0 to 120 h, whereas for plasma the time period to the last detectable docetaxel sample was used.

Toxicity

Toxicity and other complications were recorded in all CHPPC procedures in which docetaxel was administered. Hematological, cardiac, renal and other drug-related toxicity was evaluated according to WHO criteria.

Results

Patient characteristics

Eighteen women underwent cytoreductive surgery and CHPPC with docetaxel for peritoneal carcinomatosis. One patient was treated twice by this modality. Fifteen patients had epithelial ovarian cancer, while an endometrial carcinoma, a uterine Muellerian tumor and a uterine adenocarcinosarcoma were the primary malignancies in one case each. At the time of treatment the patients varied from 51 to 80 years of age, with a mean and median age of 64 years. Fifteen patients were heavily pretreated with systemic chemotherapy, receiving an average number of 10 chemotherapy courses. Two patients had received also CHPPC with cisplatin and, as previously mentioned, one patient received for the second time CHPPC with docetaxel. Samples for this pharmacokinetic study were obtained in eight cases, while a complete set of samples was collected in five patients. The characteristics of those patients are summarized in Table 1.

Cytoreductive surgery and CHPPC

Optimal surgical cytoreduction, leaving no tumor noduli larger than 0.5 cm behind, was achieved in 16 of the 19 procedures, while this was possible in seven of the eight cases with pharmacokinetic data. The surgical procedures performed, the patients' body surface area, the total administered dose of docetaxel, the initial perfusate volume and complications are noted in Table 2 for the patients with pharmacokinetic data. The mean intra-abdominal pressure varied from 12 to 23 mmHg.

Toxicity

No intraoperative complications were observed. After 12 of the 19 procedures, mostly minor, complications occurred, resulting in a morbidity rate of 63%. Wound infection was seen in seven cases with one of those developing evisceration. Transient atrial fibrillation responsive to medical treatment (grade 2) was observed in two patients. Postoperative psychosis and pelvic

Table 1 **Patients' characteristics with prior treatment and reason for CHPPC**

Patient	Age	Primary tumor	FIGO stage	Initial operative treatment	Prior chemotherapy	Clinical response	Period after last chemotherapy	Reason for CHPPC
1	66	epithelial ovarian cancer	III	HBO	9 × cyclophosphamide–carboplatin, 4 × paclitaxel–cisplatin for recurrence	CR	6 months	(second time) early i.p. recurrence
2	51	endometrial carcinoma	Ic	HBO	–	–	–	i.p recurrence
3	75	epithelial ovarian cancer	IV[a]	HBO, Om, Chol, Transv, Splen	3 × alkeran, 3 × paclitaxel–cisplatin, 10 × CAP, 17 × paclitaxel	NC[b]	5 months	refractory disease
4	72	epithelial ovarian cancer	III	HBO, Om	3 × paclitaxel–cisplatin, 6 × carboplatin, 3 × docetaxel	CR	3 months	positive SLO
5a	55	epithelial ovarian cancer	III	HBO, Om, App Chol	6 × paclitaxel–cisplatin	CR	3 months	positive SLO
5b	56	epithelial ovarian cancer			CHPPC with docetaxel, 4 × paclitaxel–cisplatin	CR	2 months	positive SLO
6	61	epithelial ovarian cancer	Ic	HBO	6 × paclitaxel–carboplatin	CR	–	consolidation
7	58	epithelial ovarian cancer	III	HBO	8 × epirubicin–cisplatin	CR	6 months	early i.p. recurrence

[a]Splenic metastases.
[b]Remission systemic metastases.
Initial operative treatment = operative treatment for primary tumour before cytoreductive surgery and CHPPC, HBO = hysterectomy with bilateral ovariectomy, Om = omentectomy, Chol = cholecystectomy, App = appendectomy, Transv = transverse colon resection, Splen = splenectomy, CAP = cyclophosphamide, adriamycin, cisplatin, CR = complete response, NC = no change, SLO = second look operation.

Table 2 **Data on cytoreductive surgery and CHPPC, docetaxel dose and postoperative complications**

Patient.	Cytoreductive surgery[a]	Optimal/suboptimal	BSA (m^2)	Total dose of docetaxel (mg)	Perfusate volume (l)	Complications
1	Om, Chol, App, cervix	OC	1.60	120	6.0	wound infection
2	Om, Chol, App, cervix	OC	2.08	160	7.5	wound infection, thrombopenia grade 2
3	Partial gastrectomy	SC	1.73	130	6.0	thrombopenia grade 2, sepsis of unknown origin, death postoperative day 9
4	Om, Splen, Chol	OC	1.47	110	6.5	thrombopenia grade 3, wound infection, atrial fibrillation
5a	Chol	OC	1.52	115	5.5	wound infection, pelvic hematoma[b]
5b	–	OC	1.58	120	7.0	–
6	Om, Chol, Splen, Pancr, Col	OC	1.60	120	4.5	–
7	LAR, Om, Splen, Chol	OC	1.88	140	7.0	wound infection

See Table 1.
[a]Besides excision peritoneal noduli.
[b]Reoperation necessary.
Cervix = resection of cervix uteri and vagina, Pancr = peripheral pancreatectomy, Col = partial colectomy LAR = low anterior rectosigmoid resection, OC = optimal cytoreduction, SC = suboptimal cytoreduction, BSA = body surface area, pod = postoperative day.

Table 3 **Peak concentrations of docetaxel in perfusate (i.p.) and plasma**

Patient	Intraperitoneal		Plasma		$C_{i.p.,\ 5\,min}/C_{plasma,\ max}$
	$C_{5\,min}$ (mg/l)	$C_{2\,h}$ (mg/l)	C_{max} (mg/l)	T_{max} (h)	
1	11.21	4.09	0.466	0.5	24.0
2	15.16	8.10	0.159	2.0	95.3
3	15.44	5.08	0.256	1.0	60.3
4	5.66	3.38	0.339	2.5	16.7
5a	2.26	1.65	0.075	4.0	30.1
5b	–	–	0.089	1.5	–
6	–	–	0.166	0.5	–
7	–	–	0.299	1.5	–
Average	9.95	4.46	0.231	1.7	45.3

$C_{5\,min}$ = concentration at 5 min after drug administration (= $C_{i.p.,\ max}$ for i.p. fluid), $C_{2\,h}$ = concentration at 2 h, C_{max} = maximal concentration.

hematoma, necessitating relaparotomy, were observed in one case each. Hematological toxicity was noted in six patients (33%), including grade 1–2 thrombopenia in four cases, grade 3 thrombopenia in one case and grade 1 leukopenia in one case. No significant renal and hepatic function disorders were observed. Increase in incidence of nausea and vomiting was not significantly increased, in comparison with major abdominal surgery without CHPPC. No other chemotherapy-related morbidity was observed. Two heavily pretreated elderly patients with large volume i.p. tumor recurrence deceased during the immediate postoperative period, resulting in a mortality rate of 10.5%. One patient died after postoperative intra-abdominal bleeding and leakage of a colorectal anastomosis, while a second patient died of Gram-negative sepsis of unknown origin in the absence of leukopenia. The mean duration of hospitalization was 13 days.

Pharmacokinetic analysis

A complete set of samples was collected in five of the eight patients for pharmacokinetic study of docetaxel delivered during CHPPC. In one of those patients no abdominal drain was left behind postoperatively, making estimation of the total i.p. drug exposure inadequate. In another case 24 h after CHPPC docetaxel was not anymore detectable in drain fluid. In the other cases drug concentrations were detectable in drain fluid for at least 4–5 days postoperatively. Docetaxel was detectable in plasma 4–24 h after i.p. administration. Intraperitoneal and plasma concentrations and AUCs as well as concentration and AUC ratios are listed in Tables 3 and 4. When the circulating perfusate volume is considered to be constant during CHPPC, 8–38% (mean 20.5%) of the total amount of initially administered drug was still present in the perfusate at the completion of perfusion.

Discussion

In primary and secondary peritoneal malignancy, a higher drug exposure to the tumor cells may be achieved by i.p. drug administration. Limited and delayed drug absorption from the peritoneal cavity and the first-pass effect from the liver result in the combination of high locoregional with low systemic drug concentrations with consequently potentially higher efficacy and limited systemic side

Table 4 Intraperitoneal and systemic exposure of docetaxel

Patient	During CHPPC (0–2 h)			During and after CHPPC (0–T_x h)				
	$AUC_{i.p.}$ (h · mg/l)	AUC_{plasma} (h · mg/l)	$AUC_{i.p.}/AUC_{plasma}$	$AUC_{i.p.}$ (h · mg/l)	T_x (h)	AUC_{plasma} (h · mg/l)	T_x (h)	$AUC_{i.p.}/AUC_{plasma}$
1	15.1	0.4202	36	15.1	2	0.5898	5.0	25.6
3	22.9	0.1624	141	143.0	120	0.2578	4.0	554.7
3	20.3	0.3225	63	146.1	96	1.3870	24.0	105.3
4	8.9	0.1736	51	–	–	1.4620	21.0	–
5a	3.8	0.0649	59	36.2	120	0.2518	6.0	143.8
5b	–	–	–	–	–	0.2304	6.0	–
6	–	–	–	–	–	0.8221	15.0	–
7	–	–	–	–		1.1070	18.0	–
Average	14.2	0.2287	70.0	85.1	84.5	0.7634	12.4	207.4

T_x = time until docetaxel is detectable.

Table 5 Drug absorption rate and average values of i.p. versus serum concentration and exposure ratios for various chemotherapeutic drugs during intraoperative hyperthermic i.p. perfusion chemotherapy for ovarian cancer (the inter-patient variation is noted in parentheses)

Drug	Dose (mg/m^2)	Drug absorption rate (%)	$C_{i.p.,\ max}/C_{plasma,\ max}$	$AUC_{i.p.}/AUC_{plasma}$
Cisplatin [32–34,51]	50–400	42–85	10–15 (2–26)	13 (1.3–107)
Carboplatin [31]	800–1200	27–77	– (8–15)	3.6 (1.9–5.2)
Mitoxantrone [29]	28	–	50 (12–600)	49 (3.6–111)
Docetaxel	75	62–92	45 (17–95)	207 (26–555)

Drug absorption rate = the decrease in total drug amount in the perfusate during CHPPC, C_{max} = maximal concentration.

effects [43]. Because of the limited penetration depth in tumor deposits of i.p. chemotherapy, this treatment should be applied only in minimal residual diseases or after optimal surgical cytoreduction [44].

The results of simple instillation i.p. chemotherapy may be impaired by limited tumor penetration and incomplete irrigation of seroperitoneal surfaces by the drug-containing solution [4,44]. Optimal exposure of the entire seroperitoneal surface to the chemotherapeutic agents may be achieved by adhaesiolysis, mobilization of the bowel and peritoneal cavity expansion [38]. The need for cytoreductive surgery and improved drug distribution has led to intraoperative application of this treatment modality. Another advantage of intraoperative use is that i.p. chemotherapy can be administered under hyperthermic conditions, which are poorly tolerated by a patient who is awake. Hyperthermia is directly cytotoxic and enhances the efficacy and penetration depth of many drugs [21]. Finally, i.p. administration of some agents, including cisplatin and paclitaxel, may cause severe abdominal pain, which is better tolerated intraoperatively [17].

Following a single i.p. administration of paclitaxel, cytotoxic levels were observed to persist within the peritoneal cavity for at least 3 days and the total exposure to the drug of the peritoneal cavity exceeded that of the systemic compartment by at least a factor of 1000 [16,17]. A similar favorable exposure ratio was found after i.p. administration of docetaxel in a rat model [20]. In comparison, this ratio does not exceed a factor of 20 for platinum compounds [43]. In the previously mentioned experimental study significant higher gastrointestinal and abdominal wall drug concentrations were achieved after i.p. delivery than after conventional i.v. administration [20]. Considering the above-mentioned data as well as the suggested taxane dose–response relationship and the lack of cross-resistance after platinum–paclitaxel combination chemotherapy, docetaxel seems to be an attractive agent for i.p. delivery in recurrent ovarian cancer. Although docetaxel is heat stable and hyperthermia seems to increase intracellular docetaxel accumulation, a potential disadvantage of their use under hyperthermic conditions is the lack of thermal enhancement for taxanes in a few *in vitro* studies [45–47]. However, another *in vitro* study [48] and two *in vivo* studies [49,50] demonstrated synergistic effect of taxanes and heat.

Agents active in ovarian cancer used in CHPPC include cisplatin, carboplatin, mitoxantrone and paclitaxel [27–34]. Pharmacokinetic analyses in CHPPC studies using cisplatin, carboplatin and mitoxantrone are summarized in Table 5 [29,31–34,51]. Unfortunately, no pharmacokinetic data from the use of paclitaxel in CHPPC are available. As far as we know, this is the first study in which docetaxel was administered during CHPPC. Therefore, being cautious with this new administration route, we administered a dose of 75 mg/m^2 docetaxel, that is similar to the one i.v. used in the initial trials with i.v. administration. Even when the entire drug amount should be absorbed from the peritoneal cavity, systemic toxicity was expected to be acceptable. When the circulating perfusate volume is considered to be constant

during the procedure, an average of 80% of the total amount of initially administered docetaxel was lost from the perfusate at the completion of 2 h CHPPC in our series. The decrease of the total drug amount in the perfusate is explained by the aimed attachment at and penetration of the peritoneal surface and its tumor deposits, attachment to other structures, and absorption from the peritoneal cavity to the systemic compartment.

Regional chemotherapy exposure advantage is best expressed by the peritoneal versus plasma AUC ratio. There exists a great inter-individual variability for this ratio in CHPPC (Table 5) [29,31–34,51]. In the reported studies the AUC for perfusate was measured only over the 90 min perfusion time and AUC for plasma was measured over 90 min or the first 24 h after drug administration. However, in clinical practice after drainage of the perfusate at the end of CHPPC a certain drug amount is left behind in the peritoneal cavity. After single-dose i.p. administration of paclitaxel, highly cytotoxic concentrations of the agent persist within the peritoneal cavity for several days [17]. For this reason we collected blood and drain samples during 5 consecutive days and calculated the AUC over this time period. In some of our patients docetaxel was detectable in abdominal drain fluid for more than 4–5 days, despite intraoperative drainage of the perfusate. Docetaxel appears to have by far the most favorable AUC ratio. In the present study, the AUC ratio varied during the 2 h of CHPPC between 36 and 141 (mean 70), while during the entire period this ratio was even more favorable for locoregional exposure, varying from 26 to 555 (mean 207). The AUC for the peritoneal cavity is averaged 13 to 27 times higher after i.p. administration of 75 mg/m^2 during CHPPC than the AUC achieved in the systemic compartment after i.v. administration of the recommended dose of 100 mg/m^2 [10,52]. Significant differences between AUC ratios reported after simple i.p. instillation chemotherapy and those observed after CHPPC may be explained by the short duration of CHPPC compared to the longer treatment duration for instillation i.p. chemotherapy.

Death occurred in two heavily pretreated elderly patients with a high volume i.p. tumor recurrence, reflecting probably poor patient selection. The remaining morbidity was mainly minor. Hematological docetaxel-induced toxicity was highly limited. The dose-limiting toxicity in phase I trials of systemic use of docetaxel was neutropenia, which was dose, but not schedule, dependent, whereas thrombopenia and anemia were not significant in these trials [10]. We noted in only one case grade 1 leukopenia, while thrombopenia documented in five patients was probably mostly related to blood loss during this major surgical procedure. Transient atrial fibrillation observed in two patients was attributed to postoperative fluid shifts and seems not to be drug-related, since continuous Holter monitoring, used in selected phase I studies, did not disclose any cardiac toxicity after i.v. administration of docetaxel [10]. Infusion-related hypersensitivity reactions, cutaneous reactions and fluid retention were observed in more than 30% of cases after i.v. administration, but its occurrence was significantly reduced by premedication [12,41]. In our cases, using corticosteroids and antihistamines perioperatively, no hypersensitivity or cutaneous reactions were observed, while fluid retention was not significantly increased in comparison with patients treated by CHPPC with cisplatin in our department. Postoperative fluid retention was probably mainly related to extensive surgery and hyperthermia. Pleural effusions or recurrence of ascites postoperatively were not observed. Neurotoxicity occurring rarely, and being mild and reversible after systemic use was not observed in our patients. Since diarrhea and nausea are generally mild and infrequent, prophylactic anti-emetics are not recommended after i.v. infusion [10]. In our series, the incidence of nausea and vomiting was comparable to other abdominal surgery. The relatively high incidence of wound complications may be at least partly explained by the potential significant delayed tissue injury of docetaxel reported after contact with skin and s.c. tissue and the perioperative administration of corticosteroids [53,54]. Additionally, a recent study in our institution has demonstrated that docetaxel has an important but reversible non-specific lymphopenic effect that seems to be associated with an increased risk for non-neutropenic infections [55].

In conclusion, this pharmacokinetic study confirms the theoretical favorable characteristics of docetaxel for use in CHPPC following cytoreductive surgery in patients with peritoneal carcinomatosis from ovarian or uterine origin. Intraperitoneal administration of docetaxel offers a large pharmacokinetic advantage as result of a high i.p. to systemic drug exposure ratio. Intraperitoneal exposure after i.p. administration of 75 mg/m^2 docetaxel exceeds many times the systemic docetaxel exposure after the recommended i.v. administration of 100 mg/m^2. Morbidity is mostly surgery related, while docetaxel-induced toxicity is minor, allowing an increase in docetaxel dosage to optimize i.p. drug exposure.

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