

Phase I Trial of Intraperitoneal Docetaxel in the Treatment of Advanced Malignancies Primarily Confined to the Peritoneal Cavity: Dose-Limiting Toxicity and Pharmacokinetics

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ABSTRACT

Purpose: The purpose of this Phase I study was to determine the maximum tolerated dose and dose-limiting toxicities (DLTs) of i.p. docetaxel and to determine the peritoneal pharmacokinetics and pharmacological advantage of this agent.

Experimental Design: Twenty-one patients with peritoneal carcinomatosis received docetaxel administered via an implanted i.p. catheter at doses of 40, 80, 100, 125, or 156 mg/m² every 3 weeks. DLTs on course 1 were used to define the maximum tolerated dose.

Results: Tumor types included gastric adenocarcinoma ($n = 7$), ovarian cancer ($n = 4$), other gastrointestinal primaries ($n = 3$), and other cancers ($n = 7$). Sixty cycles of i.p. docetaxel (median, 2; range, 1–11) were delivered. DLTs occurred in two patients at the 156 mg/m² dose level; both developed an ileus, and one patient died of neutropenic sepsis. One of five evaluable patients treated with 125 mg/m² docetaxel i.p. developed grade 4 neutropenic sepsis and stomatitis; another patient developed renal failure attributable to glomerulonephritis and grade 3 thrombocytopenia that was not judged to be dose-limiting. One of six patients receiving 100 mg/m² D, the recommended Phase II dose,

developed grade 4 neutropenia lasting <5 days. Other non-DLT treatment-related toxicities included dehydration requiring i.v. fluids, emesis, stomatitis, constipation, and abdominal pain. Best response on protocol therapy included 7 of 18 patients with stable disease for a median of 5 cycles (range, 2–11); 11 patients progressed by the first evaluation after a median of 2 cycles (range, 1–3). There were three patients inevaluable for response who received only one cycle of i.p. docetaxel (two because of patient preference and one because of adhesion formation). Pharmacokinetic evaluation revealed mean plasma areas under the curves (AUC) at 100 and 125 mg/m² i.p. docetaxel of 3.14 and 6.33 $\mu\text{M}\cdot\text{h}$ (ranges, 1.02–5.88 and 3.97–12.70 $\mu\text{M}\cdot\text{h}$), respectively; the mean peritoneal AUCs were 315 and 1063 $\mu\text{M}\cdot\text{h}$ (ranges, 250–373 and 239–2222 $\mu\text{M}\cdot\text{h}$), respectively. The mean peak plasma concentrations at 100 and 125 mg/m² i.p. docetaxel were 0.46 and 0.66 μM , and the mean peak peritoneal concentrations at those doses were 59 and 81 μM , respectively. The median and mean pharmacological advantage calculations ($\text{AUC}_{\text{peritoneal}}/\text{AUC}_{\text{plasma}}$) across all dose levels were 152 and 181, respectively (range, 18.8–367.4). The mean peritoneal 24- and 96-h concentrations were 0.9 μM (range, 0.2–1.6 μM) and <0.1 nM, respectively. The mean time that the concentration was >0.1 μM was 31.2 h (range, 27–36.5 h).

Conclusions: i.p. docetaxel can be safely delivered at a dose of 100 mg/m² i.p. every 3 weeks. This route of administration provides a significant peritoneal pharmacological advantage while delivering systemic concentrations consistent with the administration of standard i.v. doses.

INTRODUCTION

Steep dose–response relationships have been observed for epithelial neoplasms (1–3). Efforts to increase dose intensity include the i.p. delivery of chemotherapy, which enhances drug exposure in patients with peritoneal carcinomatosis, a common complication of advanced ovarian and gastrointestinal malignancies (4–6). i.p. chemotherapy confers a pharmacological advantage (defined as the ratio of the AUC⁴ of i.p. docetaxel to simultaneously determined plasma AUC) and may represent an advance in our ability to treat these neoplasms. Three recent studies documented improved outcomes in ovarian cancer patients treated with i.p. chemotherapy compared with control groups of patients treated with i.v. chemotherapy alone (7–9).

The taxane family of antineoplastic agents have activity in a variety of neoplasms. Paclitaxel was the first member of

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⁴ The abbreviations used are: AUC, area under the curve; MTD, maximum tolerated dose; DLT, dose-limiting toxicity.

this family to undergo clinical development and is a standard component of first-line combinations for ovarian cancer. Docetaxel, produced semisynthetically from the needles of *Taxus baccata*, also has significant activity in both solid tumor and leukemic cell lines (10, 11). Acting by the same unique mechanism of action as paclitaxel, docetaxel promotes the assembly of microtubules, preventing their depolymerization (12). However, subsequent investigations have demonstrated that significant differences exist between docetaxel and paclitaxel, including greater potency of docetaxel *in vitro* (13), different pharmacokinetic and pharmacodynamic profiles (14), different spectra of toxicity and activity (15), and incomplete cross-resistance (16).

The pharmacokinetics of i.v. paclitaxel and docetaxel have been carefully described, and data regarding the i.p. administration of paclitaxel have been published, (17), documenting a pharmacological advantage of up to 1000-fold. On the basis of these encouraging data regarding the potential therapeutic advantage of i.p. paclitaxel, we undertook this Phase I study, which was designed to determine the MTD, DLTs, pharmacokinetics, and possible pharmacokinetic advantage of docetaxel administered as an i.p. infusion in patients with peritoneal carcinomatosis.

MATERIALS AND METHODS

Patient Selection. Between June 1999 and February 2001, 21 patients with advanced, histologically proven malignancies primarily confined to the peritoneal cavity were entered on this Phase I trial. Patients were required to have chemotherapeutically unresponsive malignancies, to have relapsed after previous chemotherapeutic regimens, or to have malignancies for which no defined "standard" chemotherapeutic regimen exists. Patients included in the study had a Karnofsky performance status $\geq 60\%$, age ≥ 18 years, an expected survival ≥ 3 months, a serum creatinine ≤ 1.5 mg/dl or a 24-h creatinine clearance ≥ 50 ml/min, a total WBC $\geq 3,500/\mu\text{l}$ or absolute neutrophil count $\geq 2,000/\mu\text{l}$, and platelet count $\geq 150,000/\mu\text{l}$. Adequate hepatic function was defined as a serum bilirubin ≤ 1.5 mg/dl and aspartate aminotransferase and alanine aminotransferase within twice the institutional upper limit of normal. Previous radiation or chemotherapy must have been completed at least 4 weeks before beginning treatment on this protocol. There was no limit on the number of previous courses or types of chemotherapy. Female patients could not be pregnant. Patients must have been willing to undergo the necessary surgical procedure for insertion and removal of an i.p. catheter. All patients gave their voluntary informed consent and signed a consent document that had been reviewed and approved by the City of Hope National Medical Center Clinical Protocol Review and Monitoring Committee and Institutional Review Board.

Pretreatment Evaluation. All patients had a complete history and physical examination, including documentation of weight, Karnofsky performance status, presence of measurable or evaluable disease, a complete blood count with platelet count and differential, 18-channel blood chemistry analysis, CA-125 level, chest X-ray (if indicated), and computed tomographic scans of the chest, abdomen, and pelvis as needed to document

measurable or evaluable disease. In addition, all patients underwent peritoneal fluid analysis for cell count and cytology and culture for bacteria. Patients with measurable disease were required to have radiographic procedures for analysis of that measurable disease repeated no less often than every 8 weeks.

Treatment Plan. Patients were treated in cohorts of three. The starting dose of i.p. docetaxel was determined by decreasing the usual i.v. dose by 60% and subsequently escalating according to a modified Fibonacci scheme. The drug was administered by i.p. infusion at an initial dose of 40 mg/m², repeated every 3 weeks. The dosage for later cohorts consisted of 80, 100, 125, and 156 mg/m² (see Table 1 for dosage escalations), with no inpatient dose escalation. Premedications administered 1 h before docetaxel instillation included 20 mg of dexamethasone i.v., 20 mg of famotidine i.v., 25 mg of diphenhydramine i.v., and 2 mg of granisetron p.o. Dexamethasone (4 mg p.o.) was then repeated twice daily for 2 days after chemotherapy.

Docetaxel was prepared by reconstituting the available formulation in the accompanying polysorbate 80 diluent. The reconstituted preparation was then diluted in 2 liters of 0.9% saline for i.p. administration and instilled via a portacath catheter through a Huber needle. Immediately before docetaxel instillation, 500 ml of warmed saline were instilled into the peritoneal cavity and allowed to dwell for 15 min. Appropriate samples were then obtained, and the chemotherapy was instilled as quickly as possible and allowed to remain in the peritoneal cavity. Patients were turned hourly to bathe all areas of the peritoneum. No attempt was made to drain the instilled chemotherapy. After 4 h, the Huber needle was removed and the portacath was cleaned and covered with a dressing.

Patients experiencing any reversible grade 3 toxicity with stable disease or responding tumors were allowed to receive subsequent cycles of therapy at a dose reduction of one level. If a second grade 3 or any grade 4 toxicity was observed on a subsequent cycle, the patient was taken off study. Six patients required treatment delays. A minimum of three patients evaluable for toxicity were entered at each dose level before any dose escalation. Dosage escalations were determined by the toxicity encountered after the first cycle of i.p. chemotherapy. If after one complete course of therapy there were no grade 3 or 4 toxicities observed in any member of the cohort, the dosage of docetaxel was escalated by one level for the next three patients. A single instance of grade 3 toxicity resulted in the accrual of three additional patients at that dose level. If no further grade 3 toxicities were observed in the additional patients (*i.e.*, only one of six patients with grade 3 toxicity), drug doses were escalated in the next cohort. A single instance of grade 4 toxicity at any dose level or a second grade 3 toxicity in the additional three patients established the MTD as at least one dose level lower. The MTD was defined as the highest dose at which no grade 4 toxicities and at most one grade 3 toxicity were encountered in a six-patient cohort. Standard WHO response criteria were used in patients having measurable or evaluable disease (18). Toxicity was measured by the Common Toxicity Criteria of the National Cancer Institute, Version 2.0 (January 30, 1998).

Plasma Sampling. Immediately before initiation of docetaxel administration, in a subset of patients at each dose level,

Table 1 Dose levels and number of courses

Dose level	Dose (mg/m ²)	Courses per patient, median (range)
1	40	4 (3–5)
2	80	3 (1–6)
3	100	2 (1–11)
4	125	2 (1–8)
5	156	1

Table 2 Patient characteristics

Gender (F/M)	10/11
Race	
Caucasian	17
Asian	4
Histological types	
Gastric cancer	7
Ovarian cancer	4
Other gastrointestinal cancers	3
Other cancers	7
Karnofsky performance status	
90–100%	11
70–80%	8
60%	2
Median (range) age (years)	59 (35–79)

samples were collected for pharmacokinetic analysis. Blood was collected into two 4-ml heparinized tubes (green-top) and immediately placed on ice. The samples were separated, and the plasma was frozen within 1 h. One additional 4-ml heparinized tube of blood was collected immediately on completion of the docetaxel infusion (hour 0) and at hours 1, 2, 4, 6, 8, 12, and 24 after completion of the infusion of the docetaxel and were similarly processed. Ten ml of peritoneal fluid were simultaneously withdrawn from the peritoneal catheter at the time of each plasma sample collection for i.p. docetaxel levels and were processed similarly.

Analysis of Docetaxel Concentrations. The docetaxel concentrations in plasma and peritoneal fluid were measured according to a modification of a previously published high-performance liquid chromatography method (19). Briefly, after the addition of cephalomannine (Sigma Chemical Co., St. Louis, MO) as an internal standard, sample clean-up was performed

using a 1-ml cyano solid-phase extraction cartridge (J.T. Baker, Phillipsburg, NJ). Chromatographic separation was achieved with isocratic elution across a C₁₈ analytical column using a mobile phase consisting of 42.5% acetonitrile in water. Docetaxel and the internal standard were detected by UV absorbance at a wavelength of 230 nm. Data were calculated against defined standard curves generated in either donor plasma or pretreatment peritoneal fluid using Shimadzu Class-VP software (Shimadzu Scientific, Columbia, MD).

Pharmacokinetic Calculations. Estimates of total docetaxel exposure ($\mu\text{M}\cdot\text{h}$) in both peritoneal fluid and plasma were defined as the AUC. Noncompartmental methods were used to estimate the AUCs over the interval beginning with fluid instillation and extrapolated to infinity by use of an elimination rate constant derived from a weighted least-squares fit of the last four measured concentrations. The pharmacological advantage was calculated as the docetaxel $\text{AUC}_{\text{peritoneal}}/\text{AUC}_{\text{plasma}}$. Peak plasma and peritoneal fluid docetaxel concentrations (μM) were defined as the highest measured drug levels.

Statistical Methods. This Phase I trial was designed to establish the MTD and the DLT of docetaxel administered as an i.p. infusion. The dose levels are provided in the treatment plan section above. The DLT in a given patient was defined as any grade 3 or 4 nonhematological toxicity (with grade 3 mucositis being an inability to eat or drink), grade 4 thrombocytopenia, or grade 4 neutropenia lasting more than 5 days or associated with fever. To be evaluable for toxicity, a patient must have received at least one treatment and have been observed at for at least 2 weeks after the first course or have experienced DLT. All patients who were not evaluable for toxicity were replaced.

Table 4 Plasma pharmacokinetics

Dose	Mean plasma AUC		Mean plasma peak concentration	
	ng/ml·h	$\mu\text{M}\cdot\text{h}$	ng/ml	μM
40 (<i>n</i> = 2)	960	1.13	82.5	0.1
80 (<i>n</i> = 3)	2303	2.70	197	0.23
100 (<i>n</i> = 5)	2680	3.14	389	0.46
125 (<i>n</i> = 6)	5405	6.33	566	0.66
156 (<i>n</i> = 2)	6900	8.08	457	0.53

Table 3 Cycles, responses, and DLTs of therapy

Dose (mg/m ²)	No. patients treated	No. patients excluded from course 1 toxicity evaluation	Total no. of cycles (range)	No. of DLTs	DLT description	Best response during therapy
40	3	0	12 (3–5)	0	NA ^a	2 SD 1 Prog
80	3	0	10 (1–6)	0	NA	1 SD 2 Prog
100	6	0	19 (1–11)	1	Grade 3 nausea/vomiting/ileus/dehydration/hypertension	2 SD
125	7	3	17 (1–8)	1	Grade 4 ileus/sepsis	1 Prog 2 SD
156	2	0	2	2	Ileus/sepsis grade 5 (1)	5 Prog 2 Prog

^a NA, not applicable; SD, stable disease; Prog, progression.

Table 5 Peritoneal pharmacokinetics

Dose	Mean peritoneal AUC		Mean peak peritoneal concentration		Mean AUC _{peritoneal} /AUC _{plasma}	Mean (range) peritoneal concentration (μM)		Mean (range) time $>0.1 \mu\text{M}$ (h)
	ng/ml·h	$\mu\text{M}\cdot\text{h}$	ng/ml	μM		24 h	96 h	
40 ($n = 1$)	121,300	142	17085	20	126	1.1	<0.01	37.5
80 ($n = 2$)	631,437	739	43392	51	206	9.0 (2.1–18.1)	419 (0.2–837)	97.25 (47–147.5)
100 ($n = 3$)	269,053	315	50429	59	108	0.9 (0.2–1.6)	<0.01	31.2 (27–36.5)
125 ($n = 5$)	908,061	1,063	69162	81	214	17.5 (2–41.5)	245.5 (<0.1 to 1162.6)	75.9 (26–145)
156 ($n = 1$)	466,909	547	68492	80	160	13.8	0.04	44

RESULTS

Patient Characteristics. Twenty-one patients received 60 courses of treatment (Table 1). Ten patients were female; 11 were male (Table 2). The median age was 59 years (range, 35–79 years), and the median Karnofsky performance status was 90% (range, 60–100%). The tumor types included gastric adenocarcinoma ($n = 7$), ovarian cancer ($n = 4$), other gastrointestinal primaries ($n = 3$), and one patient each with uterine sarcoma, endometrial carcinoma, cholangiocarcinoma, pancreatic carcinoma, bladder carcinoma, adenocarcinoma of unknown primary, and pseudomyxoma peritonei. All patients had previous abdominal surgery, and 13 patients had received previous chemotherapy (median number of regimens, 1; range, 0–5), and two patients had received previous radiation to the abdomen.

DLTs of Therapy. The dosage escalation scheme and toxicity by dose level are summarized in Table 3. Toxicity was mild at dose levels 1 and 2 (40 and 80 mg/m²). No DLTs were noted in the six patients enrolled. The first patient enrolled on dose level 3 (100 mg/m²) developed a self-limiting ileus accompanied by nausea/emesis, hypertension, and dehydration requiring hospitalization for 2 days. The same patient also required a red cell transfusion. Non-dose-limiting neutropenia persisting for <5 days and unassociated with fever was noted in three patients. The dose level was expanded to accrue five additional patients, none of whom experienced grade 3 or 4 toxicity. Five patients were then treated at dose level 4 (125 mg/m²). None of these patients experienced DLTs (two were inevaluable for toxicity because they missed day 8 blood counts). Two patients were then treated at dose level 5 (156 mg/m²). Both of these patients developed neutropenic sepsis and ileus. One patient died from complications of these toxicities. Two additional patients were then treated at dose level 4. One developed sepsis from a peritoneal catheter infection and was considered inevaluable for toxicity. The other patient experienced grade 4 neutropenic sepsis and grade 3 stomatitis, anorexia, diarrhea, and dehydration. No significant peripheral neuropathy, fluid retention, or nail changes were noted at any dose level.

Cycles Completed, Responses, and Reasons for Discontinuation of Protocol Therapy. The number of cycles administered and range per dose level are summarized in Tables 1 and 3. The median numbers of cycles per dose level were 4, 3, 1.5, 2, and 1 for dose levels 1–5, respectively, ranging from 1 to 11 cycles across all dose levels. Eighteen of the 21 patients treated on this study were evaluable for response. Seven patients had stable disease for a median of 5 cycles (range, 2–11). One of

these patients with microscopic residual ovarian cancer developed treatment-related abdominal cramps after two cycles and declined further i.p. docetaxel. She subsequently had an 8-month progression-free interval before developing clinically apparent recurrent disease. Eleven patients had progressive disease after a median of one cycle (range, one to three) of i.p. docetaxel. Three patients were inevaluable for response: two patients who received only one cycle of therapy and declined further i.p. therapy, and one patient who experienced portacath failure after one cycle.

Pharmacokinetics. Plasma and/or peritoneal pharmacokinetic analyses were performed on 18 patients and are summarized in Tables 4 and 5 and in Figs. 1 through 5. The mean values of the peak plasma concentrations and AUCs at the MTD of 100 mg/m² were 0.46 μM and 3.14 $\mu\text{M}\cdot\text{h}$, respectively. The mean peak peritoneal concentration and AUC were 59 μM and 315 $\mu\text{M}\cdot\text{h}$. The median and mean pharmacokinetic advantage calculations (AUC_{peritoneal}/AUC_{plasma}) across all dose levels were 152 and 181, respectively, (range, 19–367). The mean peritoneal 24- and 96-h concentrations were 0.9 μM (range, 0.2–1.6 μM) and $<0.1 \text{ nM}$, respectively. The mean time that the concentration was $>0.1 \mu\text{M}$ was 31.2 h (range, 27–36.5 h).

DISCUSSION

Increased dose intensities of chemotherapeutic agents result in improved response rates and potential survival benefit for those agents that have steep dose–response relationships against sensitive tumors (1–3). Tumors that are predominantly confined to the peritoneal cavity allow a unique opportunity to deliver increased doses of active agents directly to the area of the

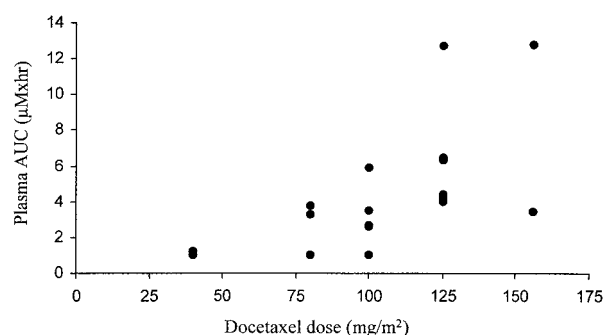


Fig. 1 Plasma AUCs plotted against dose.

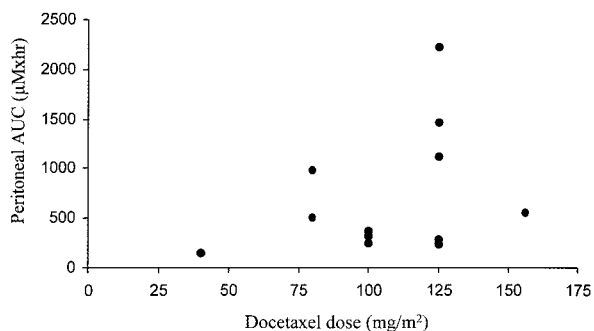


Fig. 2 Peritoneal AUCs plotted against dose.

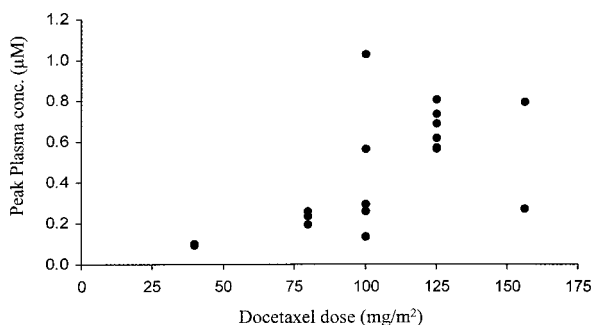


Fig. 3 Peak plasma concentrations plotted against dose.

greatest tumor involvement. Peritoneal advantages of up to 1000 times the concentrations possible by the i.v. route can be achieved by i.p. drug delivery (17, 20, 21). The utility of this approach has been demonstrated in patients suffering from advanced ovarian carcinoma in recent randomized trials comparing i.v. versus i.p. chemotherapy as first-line therapies in optimally debulked patients (7–9). In these studies, decreased toxicity and increased progression-free and/or overall survival were demonstrated in patients who received i.p. chemotherapy as part of their initial treatment. Results of second-line chemotherapy for ovarian cancer with i.p. floxuridine have also been encouraging, with a reported median survival of 38 months in patients with minimal residual disease after second-look laparotomy (22).

The present study was designed to define the MTD of docetaxel delivered directly into the peritoneal cavity. We have determined that the mean pharmacological advantage of docetaxel across all dose levels tested in this study was 181 (range, 18.8–367.4), which is comparable to other chemotherapeutic agents administered via the i.p. route. This advantage is less than the 1000-fold pharmacokinetic advantage reported for paclitaxel (17). This may be attributable to differential absorption characteristics for those drugs related to differences in solubility.

Intraperitoneal chemotherapy provides the ability to deliver high concentrations of a cytotoxic agent directly to the peritoneal space. Systemic concentrations of drugs are, however, achievable because of absorption of the agent through the peritoneal surfaces. The pharmacokinetic properties of docetaxel administered as a standard i.v. infusion are well described. Our

data indicate that the systemic AUCs of docetaxel administered by the i.p. route were comparable to the measured systemic AUCs of i.v. docetaxel, while also achieving a significant peritoneal advantage. Furthermore, the i.p. taxotere concentrations were well above those required for *in vitro* cytotoxicity after 1–2-h exposures (23–25) and were maintained for >24 h in all patients studied.

Patient tolerance of i.p. docetaxel in our trial at the MTD of 100 mg/m² was acceptable. Only one patient developed a self-limited ileus at this dose level with associated nausea and emesis, whereas the remaining patients had no severe acute or delayed peritoneal toxicities.

Although no objective responses were noted in our study, seven patients had stable disease, including one patient with gastric carcinoma who received 11 cycles of therapy and one patient with ovarian cancer who had a decreased CA-125 level from 44 to 23 units/ml after three cycles of treatment. One patient with a leiomyosarcoma of the uterus with multiple i.p. nodules received eight cycles of therapy with stable disease before the development of a new lesion.

On the basis of the results of this trial, we recommend that the Phase II dose of docetaxel administered by the i.p. route be 100 mg/m² repeated every 3 weeks. Further studies are planned to determine the utility of including this agent in combination i.p. chemotherapy programs.

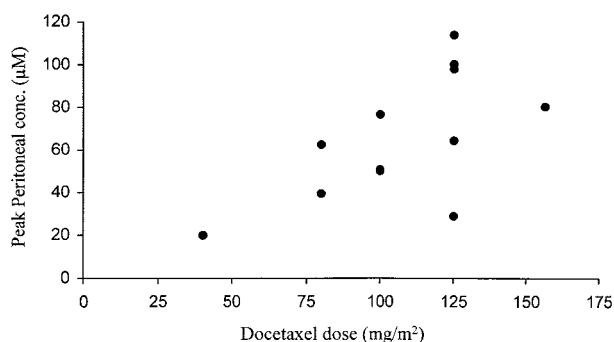


Fig. 4 Peak peritoneal concentrations plotted against dose.

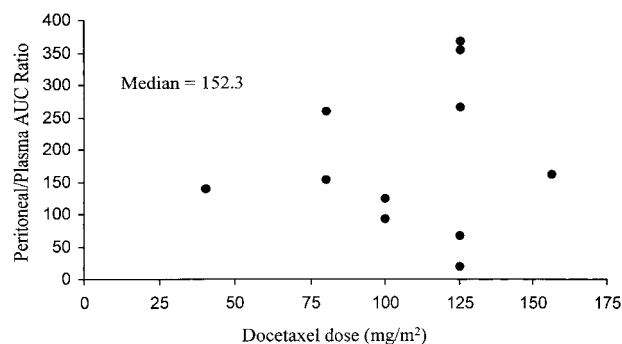


Fig. 5 Peritoneal/plasma AUC ratio (peritoneal advantage) as a function of dose.

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