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ABSTRACT

***N*-Debenzoyl-*N*-*tert*-butoxycarbonyl-10-deacytyl taxol (Taxotere, RP 56976) is a semisynthetic analogue of taxol, prepared from a noncytotoxic precursor extracted from the needles of the European yew tree (*Taxus baccata L.*). It has a broad spectrum of antitumor activity against a variety of transplantable tumors in mice. *In vitro* cytotoxicity assays suggest that it is 2–5-fold more potent than taxol. In this phase I study Taxotere was administered by 24 h i.v. infusion at 3-week intervals. Thirty patients with solid tumors refractory to conventional therapy were treated; 70 courses of Taxotere were administered at doses ranging from 10 to 90 mg/m². Grade 4 neutropenia and grade 3 mucositis were dose limiting but reversible at 90 mg/m². The pattern and grade of toxicity at this dose were similar in 3 heavily pretreated patients compared with 7 patients who had received a maximum of one previous chemotherapy regimen. Alopecia occurred at 55 mg/m² and above. Other mild toxicities included phlebitis, diarrhea, emesis, and sensory peripheral neuropathy, but these were neither dose-limiting nor clearly dose-related. One patient treated at 70 mg/m² had an anaphylactoid reaction following the second dose of Taxotere. No cardiovascular toxicity was observed. No partial or complete responses were documented. Plasma concentrations of Taxotere were determined by high-performance liquid chromatography, and end-of-fusion levels at the maximum tolerated dose exceeded drug concentrations which are cytotoxic *in vitro*. The maximum tolerated dose for Taxotere administered as a 24-h infusion is 90 mg/m².**

INTRODUCTION

Taxotere[2] (Fig. 1) is a semisynthetic analogue of taxol, which is prepared from 10-deacetyl baccatin III, a noncytotoxic precursor extracted from the needles of the European yew tree (*Taxus baccata L.*) (1). It is cytotoxic *in vitro* against murine P388 leukemia cells; the median inhibiting concentration with 72-h exposure to Taxotere is 0.004 μM compared with 0.01 μM for taxol (2). Under the same conditions Taxotere is 2.5 and 5 times more potent, as a cytotoxic, in the mouse macrophage-like line J774.2 and its taxol-resistant daughter line J7.TAX-50, respectively (2). Its mechanism of cytotoxicity is similar to that of taxol. Both drugs bind to microtubules, promote their assembly, and inhibit their depolymerization *in vitro* (2, 3). Initial *in vivo* experiments suggested that Taxotere was active against a range of transplantable murine tumors and was more active than taxol in B16 melanoma (4). *In vivo* studies in the 38 colonic adenocarcinoma have examined 4 different i.v. bolus schedules: once daily days 1 and 6; days 1, 5, 9, and 13; and days 1 to 8; and 3 times daily days 1 to 6 (4). The first two schedules allowed the administration of the largest total dose of Taxotere and, at equitoxic doses, had the greatest antitumor activity. Continuous 24-h i.v. infusions of Taxotere have not been evaluated in preclinical models and, given the clinical activity of taxol administered in this way, this schedule was chosen for a phase I study of Taxotere.

The dose which killed 10% of mice with a schedule of 5 consecutive daily i.v. doses was 300 mg/m². One-tenth of this dose (30 mg/m²) caused toxicity in dogs when administered as a single i.v. bolus. The dose causing minimal toxicity in dogs was 15 mg/m². The major toxicity observed in both mice and dogs was neutropenia. Other toxic effects included peripheral neuropathy in mice, and mucositis, emesis, diarrhea, and hair loss in dogs. Based on these preclinical studies, the phase I trial program started at a dose of 5 mg/m², one-third of the dose causing minimal toxicity in dogs. No toxicity was observed in 3 patients who received this dose as a 1-h infusion in a tandem study.[3] Therefore, we commenced the present trial with a 24-h i.v. infusion at a dose of 10 mg/m².

MATERIALS AND METHODS

Taxotere was administered as a continuous 24-h i.v. infusion, through a peripheral vein, once every 3 weeks. Patients were hospitalized for each course of chemotherapy for 24 h after the end of the infusion and closely observed for evidence of hypersensitivity reactions, hypotension, and arrhythmias. Continuous electrocardiogram monitoring was not routinely used. All patients had histologically proven cancer refractory to conventional therapy. Written informed consent was obtained from all patients, who were required to have a performance status of ≤2 on the Eastern Oncology Cooperative Group-Zubrod scale; life expectancy in excess of 12 weeks; and normal organ function, including WBC >4,000/mm³, platelets >100,000/mm³, bilirubin <25 μmol/liter, aspartate aminotransferase less than twice the upper normal limit, and serum creatinine <120 μmol/liter. No chemotherapy, immunotherapy, or radiotherapy had been given within 4 weeks of entering the study (6 weeks for nitrosoureas, mitomycin C, and wide-field irradiation); and other exclusion criteria included pregnancy, lactation, sepsis, and cerebral metastases.

All patients had a baseline history, physical examination, full blood count, biochemistry profile, urinalysis, chest radiograph, and electrocardiogram. Tumor measurements were made, where possible, using appropriate clinical or radiological methods. No other investigational drugs were administered during the study, and all concomitant medication was recorded. Patients on study were seen weekly to record toxicity and to monitor hematological and biochemical indices. Standard response criteria and WHO toxicity grading were used (5); neurotoxicity was assessed clinically and was graded according to the National Cancer Institute criteria; nerve conduction studies were not applied. Patients were withdrawn from the study after receiving 6 courses of Taxotere or if there was evidence of disease progression or life-threatening toxicity, or at the request of the patient.

The drug was supplied by Rhône-Poulenc Rorer, formulated as a concentrated sterile solution containing 15 mg/ml Taxotere in 50% polysorbate 80 and 50% dehydrated alcohol. Immediately prior to administration the drug was diluted in 1000 ml 5% dextrose, providing a polysorbate 80 concentration of <2%. The drug was delivered by continuous i.v. infusion over 24 h by a rate-minder pump (Critikon, Ascot, UK). During the first course of Taxotere, blood and urine samples for pharmacokinetic studies were collected. Blood was taken from each patient through a heparinized cannula in the opposite arm from the injection site; samples (5 ml) were collected in lithium heparin tubes before, during, after the 24-h infusion. The blood was centrifuged immediately, and the plasma was collected and stored at −20°C until analysis. Plasma and

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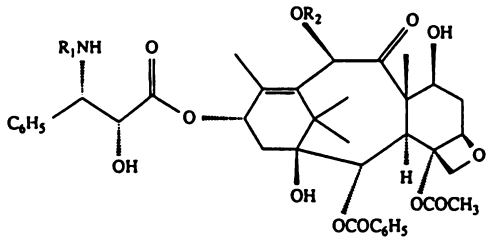
[2] The abbreviations used are: Taxotere, *N*-debenzoyl-*N*-*tert*-butoxycarbonyl-10-deacytyl taxol (RP 56976); AUC, trapezoidal area under the plasma drug concentration-time curve; MTD, maximum tolerated dose; HPLC, high-performance liquid chromatography.

[3] Marty, personal communication.



Taxotere : R_1 = -COOC(CH$_3$)$_3$; R_2 = H

Taxol : R_1 = -COC$_6$H$_5$; R_2 = -COCH$_3$

Fig. 1. Molecular structures of Taxotere (RP56976) and taxol.

urine Taxotere concentrations were measured by solid-phase extraction and reverse-phase HPLC. The drug was extracted from plasma by solid-phase extraction using C_2 (1 ml) Bond Elut cartridges (Analytichem). The cartridges were solvated prior to use with 1 ml methanol and 1.5 ml water before plasma or urine samples (0.5 ml) were applied. The plasma and urine contaminants were washed to waste with 1 ml water and 1 ml 50% methanol, and Taxotere was eluted in 250 µl 90% methanol. One hundred µl of the isolate were injected onto the column. An internal standard, taxol, was added to all samples before extraction (500 ng in 50 µl methanol/sample). The HPLC system consisted of a pump (Hewlett Packard HP1090), a variable-wavelength UV detector (Hewlett Packard 1040), a chromatography control module (Hewlett Packard 85B), and an S5 ODS2 reverse-phase column, 25 cm x 4.6 mm, with 5-µm particle size packing (Spherisorb, Queensferry, UK). The mobile phase comprised 67% methanol and 0.1% orthophosphoric acid, at a flow rate of 1 ml/min. Peak identity was confirmed by diode array detection over the wavelength range 200–500 nm, and quantitation of Taxotere was carried out by peak area integration at 225 nm. The HPLC assay for Taxotere demonstrated linearity over the range 15–500 ng/ml (r = 0.97); the intraassay coefficient of variation was between 7 and 13% over the range 15–500 ng/ml. The lower limit of quantitation of Taxotere in both plasma and urine was 15 ng/ml.

The plasma concentration-time data were analyzed by the process of nonlinear least-squares regression using an in-house computer program based on the Marquhardt algorithm (STATIS 3; Clydesoft, Glasgow, Scotland), which derived the pharmacokinetic parameters: elimination half-life ($t_{1/2}$), volume of distribution (V_d), AUC, and clearance from plasma.

Thirty patients were entered into the study; their characteristics and tumor types are summarized in Table 1. The starting dose was 10 mg/m^2, and the dose escalation subsequently followed a modified Fibonacci scheme (Table 2). A minimum of 3 patients were treated at each dose level. When grade 2 or worse toxicity was observed, at least 6 patients were entered at the same dose before further dose escalation. The MTD was defined as the highest dose which could be administered to a patient, producing severe but manageable and reversible toxicity. Nonhematological toxicity of grade 3 or worse in more than 50% of patients was not acceptable, but grade 3 or 4 neutropenia was deemed tolerable if it was not associated with fever and recovered within 1 week. Dose reductions were not planned, and there was no escalation of dose for individual patients. Response was assessed after every 2 courses of Taxotere, and in patients who had prolonged toxicity but showed evidence of response, subsequent courses were delayed until toxicities had resolved.

RESULTS

Toxicity. Thirty patients received a total of 70 courses of Taxotere, and all patients were evaluable for toxicity. The numbers of patients treated and courses administered at each dose level are summarized in Table 2, and the major toxicities observed after the first and subsequent courses are detailed in Tables 3 and 4. Six patients received more than 3 courses of Taxotere, and there was no evidence of cumulative toxicity within this subgroup.

Grade 2–3 alopecia occurred at 55 mg/m^2 and above, but other toxicities were infrequent and mild at doses of 10 to 55 mg/m^2. Leukopenia and mucositis were both dose related and dose limiting. The median nadir neutrophil counts at each dose level are summarized in Table 5. At 90 mg/m^2 neutrophil counts had fallen to their nadir by day 7 but in general recovered by day 14, and no treatments were delayed because of persisting neutropenia at day 21. Despite the short duration of neutropenia, 3 episodes of pyrexia associated with neutropenia occurred at 90 mg/m^2; all 3 also had grade 3 mucositis. These patients were hospitalized and given antibiotic therapy, but one patient died of an unresolving pneumonia. At 90 mg/m^2 one patient had grade 1 and another grade 2 thrombocytopenia. Significant mucositis (grades 2 and 3) at this dose was characterized by painful oral erythema progressing to ulceration in 8 of 21 courses (6 of 10 patients). The oral reactions started within 48 h of completion of the Taxotere infusion and healed over 3–10 days. Prophylactic mouthwashes and the anticandidal agent nystatin did not prevent this toxicity.

Patients treated at the MTD were subdivided into heavily pretreated (2 or more previous regimens) and lightly pretreated (only one previous regimen) groups, and the pattern of toxicity was compared (Table 6). The degree of toxicity was similar in the two groups.

Other toxicities were sporadic and mild. These included anemia, emesis, diarrhea, sensory peripheral neuropathy, and phlebitis. The neuropathy caused digital paresthesiae with no motor deficit. Grade 1 sensory neuropathy occurred in 2 patients at 55 mg/m^2, one patient at 70 mg/m^2, and 2 patients at 90 mg/m^2. Three of these 5 patients with sensory symptoms had previously received chemotherapy including either vincristine or cisplatin. Since only 3 patients received more than 3 courses of taxotere at 70 or 90 mg/m^2 it is uncertain whether neurotoxicity is related to the total cumulative dose of drug received. The phlebitic reactions were characterized by mild painless erythema

Table 1 *Patient characteristics*

	No. of patients
Sex	
Male	12
Female	18
Performance status (ECOG)[a]	
0	10
1	16
2	4
Age (years)	
Range	22–68
Median	55
Prior treatment	
None or surgery alone	9
Chemotherapy alone	13
Chemotherapy and radiotherapy	8
Tumor type	
Renal	6
Ovarian	5
Colorectal	5
Breast	3
Sarcoma	2
Melanoma	2
Others	7

[a] Eastern Oncology Cooperative Group.

Table 2 *Dose escalation scheme*

Dose (mg/m^2)	No. of patients	No. of courses per patient	Total no. of courses
10	3	2, 1, 2	5
20	3	4, 1, 2	7
40	3	5, 2, 3	10
55	6	2, 1, 1, 3, 6, 1	14
70	5	1, 1, 4, 2[a], 6	14
90	10	6, 2, 1, 2, 1, 2, 2, 3, 1, 1	21

[a] Course 2 discontinued after 5 min of infusion because of anaphylactoid reaction.

Table 3 *Toxicity following first course of Taxotere*

Dose (mg/m²)	Toxicity																				
	Leukopenia					Mucositis				Diarrhea				Nausea and vomiting				Anemia			
	WHO grade					WHO grade				WHO grade				WHO grade				WHO grade			
	0	1	2	3	4	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
10	2[a]	1	0	0	0	3	0	0	0	3	0	0	0	2	0	0	1	3	0	0	0
20	3	0	0	0	0	3	0	0	0	2	0	1	0	2	0	0	1	1	0	2	0
40	3	0	0	0	0	3	0	0	0	2	1	0	0	2	0	1	0	3	0	0	0
55	2	2	1	1	0	4	1	0	1	6	0	0	0	5	0	1	0	5	0	1	0
70	5	0	0	0	0	5	0	0	0	2	1	2	0	3	1	1	0	4	1	0	0
90	2	0	0	6	2	3	2	2	3	4	3	2	1	4	5	1	0	7	1	2	0

[a] No. of patients with specified grade of toxicity.

Table 4 *Toxicity following all courses of Taxotere*

Dose (mg/m²)	Toxicity																				
	Leukopenia					Mucositis				Diarrhea				Nausea and vomiting				Anemia			
	WHO grade					WHO grade				WHO grade				WHO grade				WHO grade			
	0	1	2	3	4	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
10	3[a]	2	0	0	0	5	0	0	0	4	0	1	0	4	0	0	1	5	0	0	0
20	6	0	0	1	0	7	0	0	0	5	0	2	0	6	0	0	1	4	0	3	0
40	10	0	0	0	0	10	0	0	0	9	1	0	0	6	3	1	0	10	0	0	0
55	10	2	1	1	0	8	5	0	1	14	0	0	0	11	1	2	0	7	6	1	0
70	12	1	0	0	0	10	3	0	0	10	1	2	0	8	1	4	0	8	5	0	0
90	3	2	1	13	2	10	5	3	3	10	6	4	1	11	6	4	0	14	4	3	0

[a] No. of courses associated with specified grade of toxicity.

Table 5 *Nadir neutrophil counts at each dose level*

Dose (mg/m²)	Median nadir neutrophils × 10^9/liter (range)
10	3.58 (1.98–7.91)
20	5.33 (5.18–7.62)
40	5.80 (5.18–7.62)
55	4.91 (2.10–7.19)
70	1.79 (0.32–7.02)
90	0.37 (<0.05–2.89)

Table 6 *Toxicity at 90 mg/m² in relation to prior chemotherapy*

Prior chemotherapy	Median nadir neutrophils × 10^9/liter (range)	Leukopenia					Mucositis			
		WHO grade					WHO grade			
		0	1	2	3	4	0	1	2	3
1 or 0 regimens	0.48 (<0.05–2.89)	1[a]	2	3	6	1	5	4	3	2
2 or more regimens	0.34 (<0.05–0.67)	0	0	0	8	1	4	3	0	1

[a] No. of courses associated with specified grade of toxicity.

over the course of the vein, lasting 2–3 weeks after the infusion, and were often followed by localized desquamation at the infusion site. This venous toxicity was observed in 9 of 30 patients at all dose levels above 20 mg/m² and did not preclude further treatment in any of these patients. A desquamating skin rash affecting the palms and soles occurred in one patient after 3 courses at 90 mg/m².

An anaphylactoid reaction occurred in one patient at 70 mg/m². Her first course of Taxotere was interrupted after 15 h because of a pyrexia (38°C). It was uncertain whether this was drug or tumor related, and 4 weeks later a second course of Taxotere was commenced. Within 5 min of the start of the infusion the patient became flushed, developed a tachycardia (sinus rhythm, rate 120/min), and complained of severe neck and low back pain. All of these phenomena resolved spontaneously within 30 min of stopping the infusion. The patient was already taking 10 mg/day prednisolone, and it was deemed clinically unsafe to administer any further infusions of Taxotere.

No cardiovascular toxicity was observed. One patient suffered an uncomplicated inferior myocardial infarction 1 week after his first course of Taxotere at 70 mg/m². Although there was no previous history of ischemic heart disease, this patient was a heavy smoker with a family history of coronary artery disease. Another patient developed atrial flutter, with 2:1 block, 24 h after the completion of his first course of Taxotere at 90 mg/m². The supraventricular tachycardia proved resistant to therapy, and a subsequent echocardiogram showed evidence of pericardial metastatic involvement.

One patient with renal carcinoma, treated with 90 mg/m², became icteric 8 days after the first course. This occurred in association with neutropenia and sepsis, but there was no evidence of intravascular hemolysis. Her pretreatment indices were: bilirubin, 15 μmol/liter; alkaline phosphatase, 650 IU/liter; aspartate aminotransferase, 30 IU/liter; serum glutamine-pyruvic transaminase, 66 IU/liter; and γGT, 83; and 7 days after treatment these were 270 μmol/liter, 445 IU/liter, 25 IU/liter, 58 IU/liter, and 74 IU/liter, respectively. The patient died of an unresolving pneumonia, but autopsy revealed no obvious cause for the jaundice. There was no biliary obstruction or hepatic metastases, and histological examination of the liver was unremarkable, with no evidence of intrahepatic cholestasis or drug-induced hepatitis. No pharmacokinetic data are available on this patient. No other patients in the study had drug-related hyperbilirubinemia or elevation of hepatic enzymes.

No clinical responses were observed in this study. Of the 28 assessable patients, 25 had disease progression when they were withdrawn from the study, and 3 had stable disease. One patient with an unresected but nonmeasurable peritoneal mesothelioma remains well and clinically free of disease progression 11 months after treatment with 4 courses of Taxotere at 20 mg/m².

The pharmacokinetic data are summarized in Table 7. Both the end of infusion plasma drug concentration and the AUC showed large intersubject variations, although for individuals these two parameters correlated well (correlation coefficient, 0.90). The AUC was linearly related to dose up to 70 mg/m², but there was evidence of a nonlinear increase in AUC at the MTD (Fig. 2). The drug was rapidly cleared from plasma at the end of infusion, and the drug disposition in plasma was best fitted by a monoexponential model. No Taxotere metabolites were detected in plasma or urine, and a mean of 2.3% (range, 1.2–3.7%) of the dose received was excreted unchanged in the urine within 24 h of the completion of the infusion. The relationship between

Table 7 *Pharmacokinetics of Taxotere*

Dose (mg/m²)	No. of patients assessed	End-of-infusion plasma concentration (μg/ml)	AUC (μg/ml·h)	$t_{1/2}\alpha$ (h)	Central volume of distribution (liters)	Clearance (liters/h)
20	1	0.09	0.92	0.2	9.1	29.1
40	3	0.14[a]	2.19	1.2	57.0	33.0
		(0.11–0.17)	(2.14–2.24)	(0.4–2.3)	(23.4–100.6)	(29.8 37.9)
55	4	0.14	2.56	0.6	70.8	43.3
		(0.06–0.23)	(1.19–3.28)	(0.7–1.5)	(26.5–167.7)	(25.0–78.8)
70	3	0.22	3.47	0.6	36.0	33.1
		(0.15–0.33)	(2.90–4.51)	(0.5–0.7)	(29.1–40.3)	(29.1–40.3)
90	5	0.46	7.81	1.2	36.2	19.5
		(0.27–0.57)	(5.95–9.82)	(0.6 2.1)	(18.2–58.8)	(15.0–28.6)

[a] Mean (range).

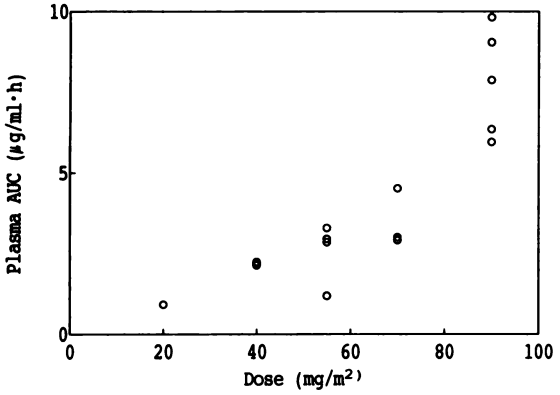


Fig. 2. Relationship between Taxotere dose and plasma AUC.

plasma AUC and the fall in neutrophils after the first course of Taxotere is shown in Fig. 3 and may be approximated by a sigmoid E_{max} (maximum fall in neutrophil count) model where C_{50} (the dose which results in 50% of the maximum effect) = 3.5 μg/ml·h and γ = 2.3. A similar model could be applied to relate the degree of neutropenia to the end of infusion plasma drug concentrations, but there was no apparent correlation between these indices of drug exposure and the severity of mucositis.

DISCUSSION

Early clinical studies with taxol have given rise to intense interest in tubulin-binding agents, following the observation of clinical activity in cisplatin-resistant ovarian cancer (6). Taxotere has a major advantage over the parent compound: it is synthesized from a precursor derived from the needles rather than the bark of the yew tree, and thus the drug source is more plentiful and renewable. Preclinical studies were generally predictive of the toxicities observed in humans, namely leukopenia and mucositis. Hypersensitivity reactions were seen in dogs treated with Taxotere and have been relatively common in clinical studies of taxol, but only one such reaction occurred in this study. It remains uncertain whether the drug or the injection vehicle is the major cause of these reactions.

The MTD, 90 mg/m², produced significant but rapidly reversible toxicity in most patients. In 3 patients the short period of neutropenia was complicated by an episode of pyrexia, which required hospitalization for therapy with antibiotics. It is likely that coincident oral mucosal ulceration (grade 3) provided the portal of entry for these infections. It has been noted that significant oral mucositis does not occur at 85 mg/m² when Taxotere is infused over 1–2 h once every 3 weeks, and a dose of 100 mg/m² produces acceptable toxicity.[3] Phase I studies with other schedules have recently been completed and are summarized in Table 8. When administered either as a 6-h infusion once every 3 weeks or as a 1-h infusion, days 1–5, every 3 weeks, the pattern of toxicity is very similar to that described here, with febrile neutropenia associated with oral mucositis (7, 8). Thus mucositis appears to be schedule dependent, but there is no evidence that the cytotoxicity of the drug is enhanced with prolonged infusions. Since the greatest dose intensity has been achieved with a 1–2-h infusion administered once every 3 weeks, phase II studies have begun with this schedule at a dose of 100 mg/m². This dose is expected to cause a brief period of grade 4 neutropenia, but in the absence of mucositis it is unlikely to lead to a significant number of septic episodes. From our study the dose which would be recommended for phase II studies with a 24-h infusion is 70 mg/m², although it may be possible to safely escalate the dose to 90 mg/m² in patients who do not develop mucositis.

Overall the patterns of toxicity observed with Taxotere and taxol are very similar (9). Neutropenia is the dose-limiting toxicity for both, and peripheral neuropathy and mucositis occur at doses around the MTD. The MTD for taxol administered as a 24-h infusion is 200–275 mg/m² (9), almost 3 times the MTD reported here with Taxotere, and although the preclinical data suggest that Taxotere is about twice as potent as the parent compound as an inhibitor of tubulin depolymerization, it is uncertain which will be the more active clinical agent.

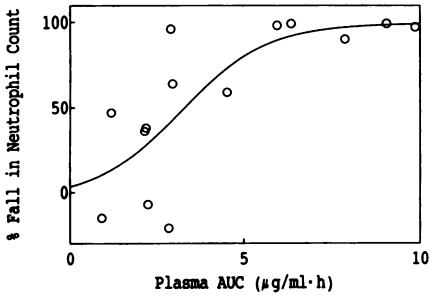


Fig. 3. Relationship between plasma AUC and the percentage relative fall in the neutrophil count following the first course of Taxotere.

Table 8 *Phase I studies with Taxotere*

Schedule	MTD (mg/m²)	Dose-limiting toxicity	Other major toxicity	Reference
24-h infusion, q 3 weeks	90	Febrile neutropenia	Mucositis	
6-h infusion, q 3 weeks	100	Febrile neutropenia	Mucositis	7
1-h infusion, days 1–5, q 3 weeks	16 × 5	Febrile neutropenia	Mucositis	8
1–2-h infusion, q 3 weeks	115	Neutropenia	Skin toxicity	10
1-h infusion, day 1 and day 8, q 3 weeks	55 × 2	Neutropenia	Asthenia	12

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