DRUG DISPOSITION

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Clinical Pharmacokinetics of Docetaxel

Stephen J. Clarke and *Laurent P. Rivory*

Department of Medical Oncology, Sydney Cancer Centre, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia

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Abstract

Docetaxel (Taxotere®), a semi-synthetic analog of paclitaxel (Taxol®), is a promoter of microtubule polymerization leading to cell cycle arrest at G2/M, apoptosis and cytotoxicity. Docetaxel has significant activity in breast, non–small-cell lung, ovarian and head and neck cancers.

Docetaxel has undergone phase I study in a number of schedules, including different infusion durations and various treatment cycles. Doses studied in adults have ranged from 5 to 145 mg/m^2 and those in children from 55 to 235 mg/m^2. The most frequently used regimen in adults is 100 mg/m^2 every 3 weeks.

A 1-hour infusion every 3 weeks has been favoured in phase II and III studies, and the disposition of docetaxel after such treatment is best described by a 3 compartment model with α, β and γ half-lives of 4.5 minutes, 38.3 minutes and 12.2 hours, respectively. The disposition of docetaxel appears to be linear, the area under the plasma concentration-time curve (AUC) increasing proportionately with dose.

Docetaxel is widely distributed in tissues with a mean volume of distribution of 74 L/m^2 after 100 mg/m^2, every 3 weeks. The mean total body clearance after this schedule is approximately 22 L/h/m^2, principally because of hepatic metabolism by the cytochrome P450 (CYP)3A4 system and biliary excretion into

the faeces. Renal excretion is minimal (<5%). Docetaxel is >90% bound in plasma.

Population pharmacokinetic studies of docetaxel have demonstrated that clearance is significantly decreased with age, decreased body surface area, increased concentrations of α_1-acid glycoproteinand albumin. Importantly, patients with elevated plasma levels of bilirubin and/or transaminases have a 12 to 27% decrease in docetaxel clearance and should receive reduced doses.

Although docetaxel is metabolised by CYP3A4, phase I combination studies have not shown major evidence of significant interaction between docetaxel and other drugs metabolised by the same pathway. Nevertheless, care should be taken with the use of known CYP3A4 inhibitors such as erythromycin, ketoconazole and cyclosporin. Conversely, increased doses may be required for patients receiving therapy known to induce this cytochrome (e.g. anticonvulsants).

Preliminary data suggest the erythromycin breath test, an indicator of CYP3A4 function, is a predictor of toxicity after treatment with docetaxel. Such methodologies may eventually enable clinicians to individualise doses of docetaxel for patients with cancer.

Docetaxel (Taxotere®, RP 56976) is one of the most active anticancer agents used in the treatment of solid malignancies, with significance probably comparable to that of the anthracyclines and cisplatin. It demonstrates major activity against a wide range of tumours, but is particularly promising in the treatment of breast, ovarian, non–small-cell lung, and head and neck cancers.[1]

Docetaxel is related to paclitaxel (Taxol®), which was identified in the 1970s as the cytotoxic principal in extracts of the Western yew tree *Taxus brevifolia*.[2] Scarcity of supply and difficulties in the formulation of paclitaxel prompted extensive investigations into the synthesis of other taxanes. A collaborative research project between Rhône-Poulenc and the Institut de Chimie des Substances Naturelles in France led, in 1981, to the discovery of a new active taxane derivative, docetaxel. Docetaxel is produced semisynthetically from 10-deacetyl baccatin III, an inactive precursor which is then esterified with a synthetic side chain. An advantage of this procedure is that 10-deacetyl baccatin III can be extracted from the needles of the European yew, a renewable resource.

The taxanes are a novel class of anticancer drugs and act as promoters of microtubule polymerisation.[3] Tubulin is normally present in cells in a dynamic equilibrium between tubulin dimers and microtubules. By promoting polymerisation, the taxanes cause an accumulation of disorganised microtubules which are resistant to disassembly by physiological stimuli. This leads to a variety of effects on dividing cells, including cell cycle arrest in G_2/M, apoptosis and acute cytotoxicity.

Docetaxel has been shown to be superior to paclitaxel in a number of preclinical models and this may be because of improved cellular uptake and increased potency of microtubule stabilisation.[4,5,6] This review examines the clinical pharmacokinetics of docetaxel and their role in the use of this drug in single or combination chemotherapeutic regimens.

1. Physicochemical Properties of Docetaxel and Formulation

Docetaxel [4-acetoxy-2α-benzoyloxy-5β,20-epoxy-1,7β,10β-trihydroxy-9-oxotax-11-ene-13α-yl-(2*R*, 3*S*)-3-*tert*-butoxycarbonyl-amino-2-hydroxyphenylpropionate] differs from paclitaxel in 2 positions (see figure 1). It has a hydroxy functionality at C-10 instead of the acetate ester found in paclitaxel and the bulky phenylpropionate side chain has a *tert*-butyl substitution attached by means of a carbamate linkage. The loss of the acetate ester at the C-10 position is probably a major

factor in increasing its solubility relative to that of paclitaxel. Nevertheless, it remains largely insoluble in water, but soluble in polar organic solvents and 0.1 mol/L NaOH or HCl. The modifications of the side chain provide docetaxel with improved tubulin binding and antitubulin activity *in vitro*.[7] The side chain contains 2 chiral centres and docetaxel is synthesised in the 2*R*,3*S*- configuration.

Docetaxel is a white to almost-white powder with an anhydrous molecular weight of 807.9 (861.9 as the trihydrate) and the chemical formula $C_{43}H_{53}NO_{14}$ (see figure 1). Docetaxel was initially provided in a 50 : 50 (v/v) mixture of ethanol and polysorbate 80 (Tween® 80) with a concentration of 15 g/L and this formulation was used in the early phase I trials. Drug was diluted in 5% dextrose to a concentration ≤0.3 g/L to ensure that the polysorbate 80 concentration did not exceed 1% as concentrations greater than this had resulted in haemolysis in canine studies.[8]

The current formulation is that of a clear brown to brown-yellow concentrate in polysorbate 80 with a concentration of 40 g/L. This concentrate is first diluted in solvent (13% m/v ethanol) before being further diluted in saline or dextrose saline. This second formulation was found to be pharmacokinetically equivalent to the initial mixture in phase I studies.[9] When stored in the dark and at 4°C, the current formulation is stable for 12 to 15 months depending on the vial size. Solutions for infusion are prepared fresh prior to administration.

Concern that the polysorbate 80 might play a role in the toxicological profile of docetaxel has recently led to the development of a submicronic dispersed formulation which is free of polysorbate 80.[10] This product is currently undergoing clinical evaluation.

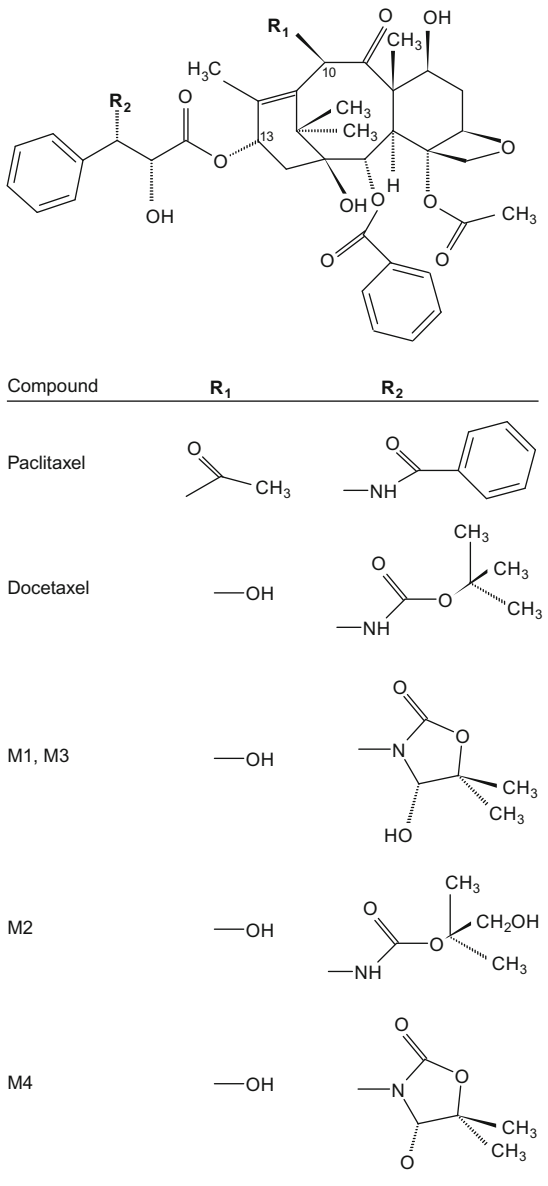

Fig. 1. Structure of docetaxel and its principal metabolites.

2. Bioanalysis of Docetaxel

In general, concentrations of docetaxel in plasma and tissue homogenates are determined by high performance liquid chromatography (HPLC) using ultraviolet detection (225 to 230nm). The internal standard used in most studies has been paclitaxel, although 2′-methyl paclitaxel has been advocated more recently.[11] The first methods described used solid phase extraction on C2 columns following dilution of the plasma sample in acetonitrile/water.[12,13] The chromatography was performed on a C-18 column under isocratic conditions. The

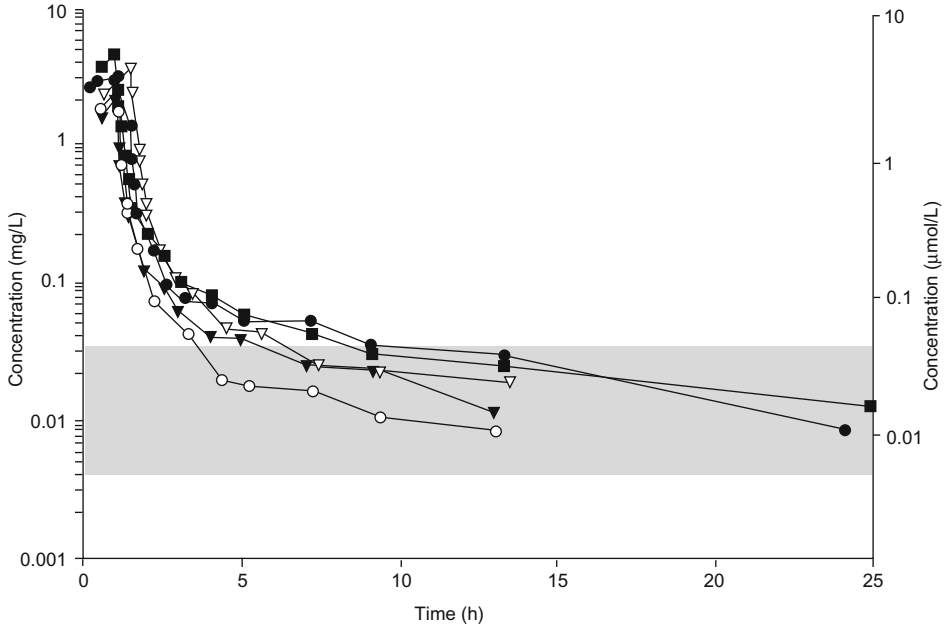

Fig. 2. Pharmacokinetics of docetaxel in 5 representative patients following 1- to 2-hour infusions at 100 mg/m^2. The abscissa is labelled in both mg/L (**left**) and µmol/L (**right**). The shaded area represents the range of concentrations required to inhibit cell growth by 50% (IC_{50}) reported for several cell lines.[5]

limit of detection was reported as being 10 µg/L. At the recommended dose of 100 mg/m^2, concentrations of this order of magnitude are observed 5 to 24 hours after a 1- to 2-hour infusion (fig. 2).

The sensitivity of HPLC assays was particularly problematic in phase I trials where the starting doses were as low as 5 mg/m^2, and it is likely that some of the pharmacokinetic inconsistencies noted in these studies were at least partly because of assay limitations. Newly established methods have used liquid-liquid[14] or solid-phase[11] extraction to improve the robustness of the assay. However, the limit of quantification remains of the order of 5 to 10 µg/L. Docetaxel in plasma samples has been shown to be stable for over 6 months when stored at –20°C.[13] At room temperature, the plasma stability of docetaxel is approximately 95% after 24 hours.[11] As part of an investigation of the possibility of intravesical administration of docetaxel, the stability of this taxane in urine at 37°C was studied and found to be approximately 90% after 4 hours.[15]

3. Preclinical Pharmacology of Docetaxel

3.1 Plasma Pharmacokinetics in Animals

The pharmacokinetics of docetaxel were evaluated in a number of species prior to clinical testing.[16] In normal and tumour-bearing mice, the plasma pharmacokinetics of docetaxel were biphasic with half-lives of 7 minutes and 1.2 hours.[12] Both the maximum concentration and the area under the plasma concentration-time curve (AUC) increased proportionately with dose over the range 13 to 62 mg/kg.[4] The total body clearance was 2.2 L/h/kg at the 37 mg/kg dose, whereas the corresponding volume of distribution at steady state (V_{ss}) was 2.2 L/kg, indicating appreciable tissue uptake and binding. The AUC at the maximum tolerated dose (MTD) in mice was found to be 17 mg/L · h,

which is approximately 3-fold higher than that observed in clinical studies (approximately 5 mg/L · h at 100 mg/m^2 – see section 4).

The kinetics of docetaxel in rats have also been described as being linear over the clinically relevant range of doses, although there was a trend towards decreased clearance at the highest concentration (20 mg/kg).[16,17] This is consistent with the nonlinear elimination of docetaxel by the isolated perfused rat liver over the concentration range 5 to 50 μmol/L.[18]

In dogs, administration of docetaxel 30 mg/m^2 over 10 minutes yielded biphasic pharmacokinetics with plasma half-lives of 4 minutes and 6.6 hours. Average estimates of AUC and clearance were 1.7 mg/L · h and 17.6 L/h/m^2, respectively.[16] The dose of 30 mg/m^2 corresponds to the 'toxic-dose-high' concentration in this species,[5] and the low AUC observed (1.7 mg/L · h) is in support of heightened sensitivity of the dog to docetaxel compared with rodents (AUC at MTD in mice = 17 mg/L · h). The binding of docetaxel to plasma proteins ranges from 70 to 95% in mice, rats and dogs.[16,19]

3.2 Tissue Kinetics and Biodistribution in Animals

The kinetics and biodistribution of [^{14}C]-labelled docetaxel have been studied in mice (111 mg/m^2) and dogs (15 mg/m^2).[19] The elimination of radiolabelled docetaxel from normal tissues in mice has been shown to be biphasic with terminal half-lives of 2 to 4.5 hours. In contrast, the elimination from colon adenocarcinoma xenografts was appreciably slower, with a terminal elimination phase of approximately 22 hours. As a result, the AUC of docetaxel in tumour tissue significantly exceeded that in plasma at all doses despite the fact that the maximal concentrations in tumour were less than 10% of those in plasma.[16]

In mice and dogs, the uptake of radiolabelled docetaxel has been shown to be extensive in a range of tissues including the liver, contents of the gastrointestinal tract including the stomach, biliary tree, pancreas, muscle and haemopoietic tissues.[16] Immediately after administration, the highest concentrations of radioactivity were found in the liver, bile and intestine, consistent with hepatobiliary excretion (see section 3.3). There was no detectable uptake of radiolabelled docetaxel into the central nervous system.

The possibility of developing an oral formulation of docetaxel was investigated in mice bearing B16 melanoma xenografts. Although intravenous and intraperitoneal administration of the drug resulted in considerable activity in this model, oral administration was associated with a total lack of activity, perhaps because of the intragastric degradation of the drug.[16] However, the demonstration of P-glycoprotein–mediated efflux by intestinal cells[20] raises the possibility that absorption of docetaxel in the gastrointestinal tract is limited because of the presence of this transporter.

3.3 Metabolism of Docetaxel

Pharmacokinetic studies in mice, rats and dogs have demonstrated that docetaxel is extensively metabolised.[18,19] Indeed, when [^{14}C]docetaxel was administered to rats at a dose of 30 mg/m^2, only 10% of the parent drug was recovered over 48 hours, during which time excretion was essentially complete.[18] The majority of the radiolabel was recovered in the faeces or bile, with several metabolites accounting for close to 75% of the dose injected. Similar data were obtained in clinical studies (see section 4.2). This suggests that sequential metabolism and biliary excretion are the principal pathways of excretion of docetaxel. In this respect, docetaxel is similar to paclitaxel.[21]

The major metabolites of docetaxel have been identified and synthesised.[18,22,23] The principal site of metabolism is the *tert*-butylpropionate side chain which undergoes a series of oxidation reactions beginning with the oxidation of one of the methyl groups (M2, fig. 1). This is probably followed by spontaneous cyclisation of putative unstable aldehyde and acid metabolites of the alcohol to 2 diastereoisomers (M1 and M3) and a ketone metabolite (M4). There is no evidence of the formation of glucuronide or other conjugates.

Unlike for paclitaxel, oxidation of the taxane nucleus and the C-3′ phenyl of the C-13 side chain does not take place to any significant extent.[24] Also, there is little interspecies difference in the spectrum of metabolites produced.

Correlations between the production of the *tert*-butyl alcohol and *N*-erythromycin demethylation and 6β-testosterone hydroxylation in human liver microsomes implicate cytochrome P450 (CYP)3A in the metabolism of docetaxel in humans.[24-26] This is supported by inhibition studies carried out with ketoconazole, troleandomycin and antibodies to CYP3A. Apparent Michaelis-Menten kinetics observed using human microsomes have been characterised in 2 studies with Michaelis-Menten constant (Km) values of 1.1 and 2.1 μmol/L.[24,25] In both human and rat liver microsomes, there was some evidence for the involvement of an additional low-affinity CYP isoform able to metabolise docetaxel.[25]

All 4 of the principal metabolites of docetaxel have greatly reduced cytotoxic activity against cancer cell lines *in vitro* and *in vivo* as well as against human bone marrow isolates.[22,27]

4. Clinical Pharmacology of Docetaxel

4.1 Protein Binding

In human plasma at 37°C and pH 7.4, docetaxel was found to be more than 92% bound in a concentration-independent manner.[28] There was little interaction of the drug with red blood cells and the binding was not influenced by the presence of polysorbate 80 (10 to 200 mg/L). Many plasma components, including lipoproteins, albumin and α_1-acid glycoprotein (AAG), were found to bind docetaxel and computed estimates showed that high-density lipoprotein, albumin and AAG were approximately equal contributors. However, because of the variability of concentrations of AAG observed in patients, it was considered that this component of binding would contribute the most to interpatient variability in the free fraction of docetaxel, accounting for a maximal 2-fold change over the range of AAG concentrations observed clinically.

4.2 Radiolabelled Excretion Studies

A study of the biodistribution of [^{14}C]-labelled docetaxel (with 100 mg/m^2 of unlabelled drug) in 3 patients demonstrated that the bulk of docetaxel is metabolised and excreted into the faeces via the bile,[29] as predicted by the animal studies. 80% of the administered dose of ^{14}C was eliminated in the faeces; only approximately 5% of radioactivity was recovered in the urine over 7 days, indicating that urinary excretion is minimal. No radioactivity was released as breath $^{14}CO_2$, but small amounts of drug were detected in the saliva.

4.3 Phase I Studies of Single-Agent Docetaxel

A number of phase I schedules of single-agent docetaxel have been explored in Europe and the US, including 1- to 2-hour,[8,30] 6-hour[30] and 24-hour[31] infusions, each repeated every 3 weeks, a 1-hour infusion administered daily × 5 days every 21 days,[32] a 1-hour infusion on days 1 and 8 of a 3-week cycle[33] and a 1-hour infusion every week for 6 weeks of an 8-week cycle.[34] Pharmacokinetic data are available for the majority of these studies and are summarised in table I.

Urinary excretion of docetaxel over 24 hours was low in all studies (<10%). A consistent feature of the early phase I studies was the absence of prophylactic premedication for the hypersensitivity reactions. If allergic reactions did occur, corticosteroids and antihistamines were used with subsequent courses.

As mentioned in section 1, a comparison of the data from phase I trials using ethanol/polysorbate 80 and ethanol-free formulations of docetaxel demonstrated similar drug exposures following short infusions.[9] Therefore no distinction on the basis of formulation will be made in our description of these early studies.

Neutropenia was dose-limiting in all but one of these studies and mucositis became problematic with the 6- and 24-hour infusions and the daily × 5

Table I. Summary of pharmacokinetic parameters from phase I studies of docetaxel

Infusion schedule	Doses examined (mg/m^2)	Numbers of patients (courses) in pharmacokinetic studies	Disposition half-lives (h)[a]			Clearance ($L/h/m^2$)[a]	AUC (mg/L • h)[a]	V_{ss} (L/m^2)[a]	Ae_{24} (%)	Reference
			α	β	γ					
1-2h every 2-3 wks	5-115	23 (25)	0.08	1	13.5	22.2	5.2	53	2.8	8
1h every 3 wks	40-145	22	NR	NR	NR	20.2	NR	NR	NR	10
1h every 3 wks[b]	55-75	NR	0.09	1.4		33.2	2.3	37	NA	35
6h every 3 wks	5-80	NR	0.05	1.1	12.4	16.0	6.8	99	2.8	30
2h every 3 wks	100-115	NR	0.07	0.9	11.4	20.0	5.2	82	2.8	30
24h every 3 wks	10-90	16		1.2		19.5	7.8	36	2.3	31
1h on days 1 and 8 every 3 wks	55	3 (5)	NR	NR	NR	28.0	2.1	72	NR	33
1h daily × 5 days every 3 wks	1-16	13	0.11[c]	3.6[c]		32.9[c]	5.8[c]	73[c]	<6	32

a Mean values at the maximum tolerated dose.

b Paediatric patients.

c Values on day 5 of a daily × 5 days schedule.

Ae_{24} = urinary excretion in 24 hours; **AUC** = area under the plasma concentration-time curve; **h** = hours; **NR** = not reported; **V_{ss}** = volume of distribution at steady state; **wk(s)** = weeks(s).

days regimen. In the weekly × 6 of every 8 weeks schedule the dose-limiting toxicities were fatigue and asthenia, with only 14% of patients experiencing grade III, and no patient grade IV, leucopenia.[34] Unfortunately, in the absence of pharmacokinetic data, it is uncertain whether the apparent marrow-sparing effect of the weekly regimen is because of a modification of drug disposition or due to pharmacodynamic changes.

The phase I studies investigated doses ranging from 5 to 145 mg/m^2. The starting dose of 5 mg/m^2 represented a third of the 'toxic-dose-low' in the dog.[5] In the study of Extra et al.,[8] docetaxel was administered as a 1- to 2-hour infusion initially every 2 weeks but subsequently every 3 weeks after the occurrence of toxicity. Plasma concentrations of docetaxel were not detectable at doses of 5 and 10 mg/m^2. Because of the limitations of the assay, the disposition appeared biphasic at doses between 20 and 70 mg/m^2 and triphasic at higher doses. Interestingly, significant drug concentrations were detected in ascitic fluid taken from 1 patient.

Assay sensitivity was also a problem with the 6-hour infusion schedule, and plasma docetaxel concentrations were near the limit of detection 2 to 3 hours post-infusion.[30] Between the doses of 5 and 20 mg/m^2, only the mean concentration during the infusion could be measured. The apparent dose-dependence of clearance observed with the 24-hour infusion schedule[31] may also be caused by assay limitations. In the case of Pazdur et al.,[32] who studied the administration of docetaxel daily × 5 days, the large interpatient variability in the estimated AUCs may have caused a bias towards the larger clearance values. For example, an estimation of clearance at the 12 mg/m^2 dose from the corresponding average AUC yields a value of only 21.2 $L/h/m^2$ as compared with the reported value of 52.2 ± 52.6 $L/h/m^2$. Importantly, the pharmacokinetic parameters obtained on days 1 and 5 were not significantly different, indicating a lack of accumulation or metabolic induction.

In spite of these technical limitations and the presence of considerable interpatient variation, there is strong evidence to suggest that the disposition of docetaxel in patients is linear with dose.[9] Nevertheless, the use of models which include terms for nonlinear elimination and disposition have recently been shown to provide improved fits of pharmacokinetic data, particularly those obtained with long infusion (>6 hours) regimens.[36]

Table II. Summary of representative pharmacokinetic data for docetaxel administered as short infusions of 1 to 2 hours

Parameter	Mean
Total body clearance (L/h/m^2)	21[a]
Area under the plasma concentration-time curve (AUC) [mg/L • h]	2.8[a]
Initial volume of distribution (L/m^2)	3.4
Volume of distribution at steady state (V_{ss}) [L/m^2]	73.8[a]
Disposition half-lives	
α (min)	4.5[a]
β (min)	38.3[a]
γ (h)	12.2[a]
Protein binding (%)	≥90
Urinary excretion in first 24h (%)	<10
Faecal excretion in first 48h (%)	≈80

a Values from data modelled using nonlinear mixed effect modelling (NONMEM).

According to the Akaike criterion, however, the improvement in fit did not justify the inclusion of these extra terms. Because the improvement was largely limited to the time-points during the docetaxel infusion, it is possible that the apparent nonlinearity during this phase is caused by the modulation of the early disposition of docetaxel by polysorbate 80.

A reanalysis of the data obtained from 2 phase I studies using short infusions (1 to 2 hours) of docetaxel has been performed to obtain an estimate of representative pharmacokinetic parameters.[37] The plasma concentration profiles used were from 26 patients who had received docetaxel at 70 to 115 mg/m^2. Population pharmacokinetics were assessed using nonlinear mixed effect (NONMEM) and nonparametric maximum-likelihood (NPML) models. A 3-compartment model was found to provide a better fit than a 2-compartment model. The average population pharmacokinetic parameters computed for a patient aged 52.3 years with a body surface area (BSA) of 1.68m^2 are shown in table II. An initial analysis of population covariates influencing docetaxel elimination was also carried out, but this was subsequently expanded with phase II data[38] and will be discussed later in section 4.4.

In most of these phase I studies, early pharmacokinetic-pharmacodynamic correlates have been formulated and relationships have been described for the effects of pharmacokinetics, especially AUC, on neutropenia. These relationships have been modelled using maximum effect (E_{max}) equations of the type:

$$\% \text{ decrease} = \frac{(E_{max}\, AUC^{\gamma})}{AUC_{50} + AUC^{\gamma}} \qquad \text{(Eq. 1)}$$

where the percentage decrease in neutrophil count is related to the E_{max}, the AUC for half-maximal effect (AUC_{50}) and the exponent γ, which relates to the steepness of the sigmoidal curve. Estimated AUC_{50} values for the 1- to 2-hour and 24-hour infusions and the daily × 5 days infusions were 0.97, 3.5 and 0.26 mg/L • h, respectively.[8,31,32] Estimates of γ were 1.36[8] and 2.3.[31] A sigmoidal relationship was also observed with the 6-hour infusion, but the AUC_{50} value was not reported.[30]

4.4 Phase II studies

Phase II studies of docetaxel were undertaken in a large number of tumour types, including breast, small-cell and non–small-cell lung (NSCLC), ovarian, pancreatic, bladder, head and neck, renal, colorectal and gastric cancers, and melanoma and sarcoma. On the basis of the phase I data, most studies utilised a dose of 100 mg/m^2 given as a 1-hour infusion every 21 days. In Japan, phase I studies were carried out with docetaxel 10 to 90 mg/m^2 and the dose of 60 mg/m^2 administered as a 1- to 2-hour infusion every 3 weeks was selected for phase II trials.

Docetaxel is one of the first oncology drugs to benefit from the inclusion of population pharmacokinetic studies into phase II protocols. Sparse data were collected (1 to 5 samples per patient) over the first 24 hours following docetaxel administration in a randomised fashion using 4 arms of varying sampling times.[39] Data from patients in 2 phase I and 22 phase II trials of docetaxel were incorporated into the modelling process in a fashion analogous to that used in modelling the phase I data.[40] The estimates of clearance which were obtained were used to probe the relationship between the pharmacokinetics of docetaxel with the patho-

physiological and demographic parameters of this population. The final model chosen was:

$$CL = BSA\ (22.1 - 3.55AAG - 0.095AGE + 0.2245ALB)\ (1 - 0.334HEP12) \quad \text{(Eq. 2)}$$

where CL is total body clearance (L/h), AAG and ALB are the plasma concentrations of α_1-acid glycoprotein and albumin, respectively (g/L), BSA is body surface area (m^2) and AGE is the age of the patient (years). HEP12 was selected as the strongest hepatic dysfunction covariate for docetaxel clearance and represented SGOT (ALT) or SGPT (AST) >60IU and alkaline phosphatase >300IU, under which conditions HEP12 was assigned the value of 1 (default = 0). This model has also been applied to data from clinical trials of docetaxel in Japan with similar results.

Although the final model only accounted for a modest proportion of the interpatient variability, it was able to identify patients who had significant deviation from the population median CL (35.6 L/h) as a result of likely hepatic dysfunction (as reflected by elevated serum markers of liver pathology) and increased AAG. BSA was confirmed as being a dominant covariate, indicating that the clearance of docetaxel is related to this morphometric parameter. This supports the use of BSA in the individualisation of dose for patients. Although BSA is widely used for dose adjustments in medical oncology, docetaxel is the only cytotoxic agent for which there is support for this practice.[41] However, it is not known whether BSA is superior to bodyweight for adjusting dose. Because both bodyweight and BSA are highly colinear, they were not both included in the population model.[39]

An updated population pharmacokinetic analysis based on this model has been recently reported for all 24 phase II studies.[42] In this analysis, attempts were made to correlate estimates of docetaxel exposure with response rate, time to first response and time to progression. No significant relationship was found in the case of breast cancer. However, first cycle AUC was a significant predictor of time to progression in NSCLC. First course neutropenia was correlated with clearance factor (the ratio of the population mean and individual CL estimates), AUC and duration of exposure >0.20 μmol/L. Both response and neutropenia were well correlated with pretreatment AAG levels, with high baseline AAG levels associated with a lower risk of treatment-induced neutropenia. Increased exposure to docetaxel with course 1 (especially extended duration of exposure to concentrations >0.20 μmol/L) was also correlated with an increased incidence of fluid retention. This supports administration of docetaxel as a short infusion (≤2 hours).

As is evident from the population model equation, patients with significant hepatic dysfunction have a decrease in docetaxel clearance of approximately 30%.[39] In addition, these patients also appear to be at a higher risk of treatment-induced toxicity.[42]

4.5 Docetaxel Pharmacokinetics in Special Populations

4.5.1 Pharmacology of Docetaxel in Patients with Renal or Hepatic Dysfunction

There are limited data available on docetaxel pharmacokinetics in patients with renal or hepatic impairment, as these were exclusions in the phase II protocols. However, it is unlikely that docetaxel pharmacology will be altered in patients with kidney impairment as its renal excretion is responsible for less than 5% of its elimination.

As mentioned in section 4.4, the population pharmacokinetic studies enabled the identification of hepatic dysfunction as a cause of reduced docetaxel clearance, with suggestion of a 12 to 30% reduction in docetaxel clearance in patients with elevated liver enzymes.[39,43] The subsequent analysis of 1070 patients treated with docetaxel 100 mg/m^2 alone further demonstrated that patients with impaired liver function had a decreased docetaxel clearance and increased risk of toxicity.[44] These authors suggested that a trial of docetaxel 75 mg/m^2 should be carried out in breast cancer patients with impaired hepatic function. The importance of liver disease is currently being assessed prospectively in 3 groups of patients with

varying degrees of liver dysfunction due to malignancy.[45] Preliminary data suggest that the MTD of docetaxel will be close to 50 mg/m^2, and subgroup analysis will perhaps determine whether bilirubin or transaminase elevations are more important in predicting toxicity. One report has documented severe toxicity and elevated docetaxel concentrations at steady state in a patient with breast cancer treated with docetaxel 100 mg/m^2 who presented with elevated pretreatment bilirubin.[46]

Liver dysfunction (as assessed by serum biochemistry) may be particularly significant for the excretion of metabolites as these have been reported to be detectable only in the plasma of affected patients.[11] As mentioned in section 3.3, CYP3A4 is involved in the metabolism of docetaxel. Nevertheless, CYP3A4 activity may not necessarily correlate with the extent of hepatic dysfunction as assessed by serum biochemistry. For example, although a good correlation has been described between CYP3A activity, as assessed with the erythromycin breath test (EBT), and the incidence of grades 3 and 4 neutropenia,[47] there was no relationship between EBT values and either the liver function tests (serum bilirubin, ALT and AST) or the presence of hepatic metastases. If good correlations can be demonstrated between the EBT and docetaxel pharmacokinetics and toxicity, it is likely that this test may provide a more quantitative indication of the capacity for individuals to eliminate docetaxel.

Generally speaking, the presence of metastatic disease of the liver itself may not warrant dose reduction. A retrospective analysis of 547 patients has revealed that the presence of liver metastases is not associated with reduced docetaxel clearance in the absence of liver dysfunction.[39] Furthermore, safety is not compromised in this subpopulation.[48]

Therefore, it is currently recommended that docetaxel doses be reduced in patients with hepatic impairment, but further studies are required to define this more precisely.

4.5.2 Pharmacology of Docetaxel in Children

Only 2 paediatric studies of docetaxel have been reported to date.[35,49] The dose ranges explored were 55 to 150 mg/m^2 (MTD of 125 mg/m^2) without haemopoietic support[35] and 150 to 235 mg/m^2 (MTD of 185 mg/m^2) using granulocyte colony-stimulating factor.[49] Limited pharmacokinetic data are available from doses of 55 and 75 mg/m^2, and these are included in table I. The concentration-time profiles were best fitted by a 2-compartment model with distribution and elimination half-lives at the higher dose of 0.09 and 1.4 hours, respectively. The clearance appeared to be greater than in adults, with a mean value of approximately 33 L/h/m^2.

5. Drug Interactions and Combination Therapy

Drug interactions may arise as the result of altered pharmacodynamics or pharmacokinetics of the drugs involved. Pharmacokinetic interactions are usually caused by modification of tissue disposition and metabolism of the drugs. These phenomena are of particular importance in cancer chemotherapy when cytotoxic agents are used because of the increased risks of severe toxicity or decreased probability of response.

As part of the characterisation of the metabolism of docetaxel, interactions were investigated *in vitro*. Cisplatin, doxorubicin, vinblastine and vincristine did not interfere with docetaxel hydroxylation, even though the *Vinca* alkaloids are also known CYP3A4 substrates.[24,26]

Cisplatin has been shown to have a complex interaction with the expression of several CYPs in the rat in a gender-dependent manner, leading to changes in drug and steroid metabolism.[50,51] Administration of cisplatin prior to a 24-hour infusion of paclitaxel resulted in a 25% reduction in the total clearance of taxane, resulting in more profound marrow suppression.[52] However, it is not clear whether this was due to an effect on CYP expression because the modulation of cytochromes in the rat studies was found to change slowly over several days. Although a possible sequence-dependent in-

teraction in terms of paclitaxel C-6 hydroxylation was noted also for the combination of paclitaxel and carboplatin, this appeared to be related to an imbalance of liver function tests between the 2 sequence groups.[53]

In the case of the combination of docetaxel and cisplatin, several regimens have been studied. When cisplatin was administered as a 3-hour infusion followed by docetaxel as a 1-hour infusion a day later, the clearance of docetaxel (median 22.6 L/h/m^2) was no different from that observed when docetaxel was given 3 hours prior to cisplatin (median 21.5 L/h/m^2), with both values corresponding closely to those observed with docetaxel alone.[54] This implies that cisplatin modulation of CYP is either not present or not significant to the disposition of docetaxel. Interestingly, it has been suggested that the myelotoxicity of this combination is schedule-dependent, with cisplatin followed by docetaxel being better tolerated than the reverse sequence.[54] However, this has not been borne out in other studies.[55] The significant effect of the vehicles Cremophor EL and polysorbate 80 on decreasing the accumulation of cisplatin in leucocytes *in vitro* has been suggested as a mechanism for possible pharmacodynamic interaction between cisplatin and the taxanes.[56] An effect on platinum-DNA adducts in leucocytes has also been reported.[57] However, the concentrations of polysorbate 80 present in plasma at the end of docetaxel infusions are below those that can be detected using current methods,[58] and the likely impact of these findings on the clinical situation is unclear.

Cremophor EL, the vehicle used for paclitaxel formulation, has been shown to have a significant effect on paclitaxel and doxorubicin kinetics in laboratory animals,[59,60] probably through an effect on hepatobiliary excretion. Indeed, it would appear that this vehicle is responsible for the nonlinearity of the disposition of this taxane observed clinically. Thus, important pharmacokinetic effects have been observed between paclitaxel (formulated in Cremophor EL) and the anthracyclines.[61] However, although polysorbate 80 may also be capable of modifying hepatobiliary excretion of some compounds *in vitro*,[62] no significant pharmacokinetic interactions attributable to this vehicle have been observed clinically. This indicates that the choice of vehicle may have consequences for the pharmacokinetic properties of taxanes.

Anticonvulsants, phenytoin and phenobarbital in particular, are known to induce several metabolic pathways of relevance to xenobiotics. There is increased expression of CYP, CYP3A in particular, when patients are treated with these compounds. The production of the C-3′ hydroxy metabolite of paclitaxel (also known as M4), which is also mediated by CYP3A4, appears to increase in patients treated with anticonvulsants. There is a corresponding increase in CL in this group[63] and it is likely that the clearance of docetaxel will be increased in similar patient populations. Importantly, pretreatment with corticosteroids, which has been routinely utilised to decrease both hypersensitivity reactions and cumulative oedema associated with docetaxel, has no impact on the pharmacokinetics or haematological toxicities of docetaxel.[64]

Drug interactions caused by a modification in protein binding are also theoretically possible based on *in vitro* data, but are generally of limited clinical significance. In the case of docetaxel, several drugs used in cancer chemotherapy (cisplatin, dexamethasone, doxorubicin, etoposide and vinblastine) did not affect the *in vitro* protein binding of the taxane.[28]

In addition to the platinum-containing regimens already discussed in this section, trials of docetaxel in combination with other anticancer agents have been performed and the data are summarised in table III. Pharmacokinetic analyses have been performed with a number of agents, including cyclophosphamide, ifosfamide, doxorubicin, epirubicin, fluorouracil, capecitabine, topotecan, irinotecan, gemcitabine and etoposide. Unfortunately, in many cases only limited data are available.

Pharmacokinetic interactions have been suggested when docetaxel was combined with either doxorubicin[71] or etoposide.[83] No other combina-

Table III. Phase I studies of combination therapies including docetaxel

Other compound (MTD in mg/m^2 and schedule)	Maximum docetaxel dose (mg/m^2 every 3 weeks) [MTD]	Pharmacokinetic study performed [docetaxel clearance (L/h/m^2)]	Pharmacokinetic interaction?	Reference
Cisplatin (>80)	>60 (NR)	Yes (NR)	No	65
Cisplatin (75)	100 (75)	Yes (22.2)	No	55
Cisplatin (80)	75 (75)	No		66
Cisplatin (75-100 over 1h)	100 (NR)	Yes (22.4)	No	67
Cisplatin (50-100 over 3h)	100 (NR)	Yes (22.9)	No	67
Cisplatin (75-100)	100 (85-100)	Yes (21.5-22.6)	No	54
Fluorouracil (250-750)	100 (NR)	Yes (22.7)	No	67
Fluorouracil (1000 over 120h)	85 (85)	Yes (24.8)	No	68
Fluorouracil (500 over 120h)	50 (60)	Yes (NR)	No	69
Doxorubicin (>50)	>60 (NR)	Yes (NR)	No	70
Doxorubicin (50)	75	Yes	Yes (NR)	71
Doxorubicin (40-60)	50-85	Yes (28.1)	No	67
Liposomal doxorubicin (45)	75	No		72
Carboplatin (>AUC 6)	75 (>75)	No		73
Carboplatin (AUC 6)	100 (80)	Yes	No	74
Carboplatin (AUC 6)	75 (75)	No		75
Carboplatin (>AUC 7)	80 (>80)	No		76
Capecitabine (1250 on days 1-14)	100 (75-100)	Yes (NR)	No	77
Topotecan (0.75 on days 1-4)	60 (NR)	No		78
Gemcitabine (800 on days 1, 8, 15)	100 every 4 weeks (100)	No		79
Gemcitabine (1000 on day 1, 800 on day 8)	85 (85)	No		80
Gemcitabine (>2500 every 2 wks)	>50 every 2 weeks (NR)	Yes	NR	81
Gemcitabine (>3000 every 2 wks)	>75 (NR)	No		82
Etoposide (75 on days 1-3)	60 (NR)	Yes (12.6)	Yes (↓CL)	83
Cyclophosphamide (600)	85 (NR)	Yes (22.1)		67
Cyclophosphamide (800)	85 (75)	No		84
Ifosfamide (2500-5000)	75 (NR)	Yes (21.8)	No	67
Ifosfamide (5000)	85 (75)	Yes (NR)	No	85
Estramustine (280 3 times daily × 5)	90 (90)	No		86
Irinotecan (60 on days 1, 8, 15)	50 (50)	No		87
Irinotecan (140-300)	70 (NR)	Yes (26.3)	No	67
Irinotecan (250 on day 1)	70 (70)	Yes (20.7)	No	88
Mitoxantrone (20)	100 (100)	No		89
Navelbine (20 on days 1, 5 every 3 wks)	100 (75-85)	Yes (27)	No	90
Navelbine (45 every 2 wks)	60 every 2 weeks (60)	No		91
Epirubicin (75)	75 (75)	Yes	No	92

AUC = area under the plasma concentration-time curve (mg • min/ml); **CL** = clearance; **h** = hours; **MTD** = maximum tolerated dose; **NR** = not reported; **wk(s)** = weeks(s).

tion demonstrated any effect on the pharmacokinetics of docetaxel or of the other compound.

In one study of 24 patients, doxorubicin 50 mg/m^2 every 3 weeks was combined with docetaxel 75 mg/m^2 over 1 hour every 3 weeks for 2 courses after patients had received docetaxel as a single agent 3 weeks earlier.[71] Patients were then randomised to receive docetaxel immediately after (group A) or 1 hour after (group B) doxorubicin. In a fourth cycle, docetaxel was administered 6 hours after doxorubicin to permit single-agent pharmacokinetic data to be determined for the anthracycline. The results showed that prior docetaxel does not significantly modify the subsequent disposition of

doxorubicin. However, the AUC of docetaxel was increased by 50 to 70% in the final cycle, indicating a possible effect of doxorubicin on the disposition of docetaxel. Two other studies[67,70] combining docetaxel and doxorubicin, although of different design, did not demonstrate a pharmacokinetic interaction between these 2 compounds.

The combination of docetaxel 60 mg/m^2 on day 1 and etoposide 75 mg/m^2 on days 1 to 3 has been reported as resulting in a docetaxel clearance of 12.6 L/h (table III), which is considerably lower than the values encountered in most studies.[83] However, the patient numbers involved in this study were also small.

6. Future Directions

Docetaxel is one of the most important new anticancer agents developed in the last 20 years because of its broad spectrum of anticancer activity, particularly in breast and non–small-cell lung cancers, which are the most common cancers in Western women and men, respectively. The clinical pharmacology of docetaxel has not been explored as extensively as that of paclitaxel and the results of many of the studies are available only as preliminary reports. For example, the pharmacokinetics of docetaxel in the weekly regimen need to be further investigated to determine the reasons for the apparent modification in toxicological profile. Also, protracted infusions of paclitaxel have been shown to produce responses in patients whose disease had progressed with short infusions of taxanes, indicating a different profile of activity and toxicity.[92] Such regimens have not been explored with docetaxel, although they may well prove to be counter-productive because of the apparent association of mucositis and febrile neutropenia with protracted infusions of this agent. However, the different profile of activity and toxicity with protracted infusions of the 2 taxanes may also be because of the differences in pharmacokinetic behaviour, such as the nonlinearity of paclitaxel pharmacokinetics.

The population pharmacokinetic analyses undertaken with docetaxel have proven extremely informative and have provided several important leads that require further study to enable the optimal use of docetaxel in a broader patient population. Covariates such as age, BSA, liver function and baseline AAG have been shown to account for some of the interpatient variation of the clearance of docetaxel and warrant further investigation so as to achieve optimal use of this compound. With respect to liver function, a phase I study in patients with hepatocellular carcinoma could provide additional valuable information on the importance of hepatic dysfunction on the pharmacology and toxicology of docetaxel. Also, it is not entirely clear as to whether the association of increased AAG with decreased likelihood of toxicity and response is caused by an effect on docetaxel biodistribution or because of its function as an independent prognostic factor in NSCLC.[93]

Population models incorporating age, BSA and baseline AAG have been shown to account for some of the interpatient variation of the clearance of docetaxel, but these are not sufficiently predictive to use in the individualisation of doses. Dose reductions in patients with abnormal hepatic biochemistry appear to be an essential safety precaution but, even so, elevated indices of liver disease (bilirubin and transaminases) may not necessarily reflect an individual's capacity for metabolism and elimination of docetaxel. In this respect, the suggestion that CYP3A4 function, as measured by the erythromycin breath test, is predictive of toxicity induced by docetaxel warrants further investigation, including correlation with pharmacokinetics. We are currently investigating some of these avenues.

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Correspondence and reprints: Dr *Stephen Clarke,* Department of Medical Oncology, Sydney Cancer Centre, Gloucester Level 2, Royal Prince Alfred Hospital, Missenden Road, Camperdown, NSW 2050, Australia.
E-mail: sclarke@canc.rpa.cs.nsw.gov.au