REVIEW ARTICLE

Drugs 1998 Jan; 55 (1): 5-30
0012-6667/98/0001-0005/$26.00/0

The Taxoids

Comparative Clinical Pharmacology and Therapeutic Potential

Elizabeth A. Eisenhauer[1] and *Jan B. Vermorken*[2]

1. National Cancer Institute of Canada Clinical Trials Group, Queen's University, Kingston, Ontario, Canada
2. University Hospital Antwerp, Edegem, Belgium

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Summary

Paclitaxel and docetaxel are 2 compounds from the new taxoid class of anticancer agents. Both drugs are very similar in preclinical activity, mechanism of action and spectrum of clinical activity. Some subtle differences in the intracellular retention of docetaxel may account for its lack of schedule-related myelosuppression and greater potency, and may be relevant to the skin toxicity and oedema which it produces. Early data suggest that there may be differing behaviour of anthracycline/taxoid combinations with respect to cardiotoxicity.

Paclitaxel has been studied in several first-line combination therapy trials in ovarian cancer. Here, paclitaxel in combination with a platinum compound seems to have proven itself as a standard regimen. It is uncertain if docetaxel will be evaluated in this context.

An abundance of clinical data is available for both analogues in the advanced, metastatic setting of breast cancer. Both also have been compared as single agents with doxorubicin with the results suggesting paclitaxel in a 3-hour infusion is inferior to the anthracycline (in terms of response rate), and those of docetaxel suggesting it is superior to the same dose of doxorubicin. This indirect comparison

favours the activity of docetaxel; however, it is clear that in the dose/schedules studied, the taxoid compounds are not equitoxic. Either agent by itself, in the treatment of metastatic breast cancer, remains appropriate; however, lack of cumulative toxicity may make paclitaxel more attractive in some situations where prolonged administration is foreseen.

Lung cancer trials have also confirmed the activity of both agents, although docetaxel appears to have slightly more promising activity in previously treated patients than paclitaxel. Paclitaxel in combination with cisplatin has been evaluated in randomised trials as first-line treatment of non–small-cell lung cancer (NSCLC). The results of these trials taken together suggest that this combination has an impact on survival similar to other new regimens now considered 'standard' in the front-line setting in this disease.

Unfortunately, despite all the phase II data generated in numerous tumour types, little else can be said about the role of either taxoid in the 'standard' management of malignant disease. It will be some years yet before taxoid-based combinations have been evaluated sufficiently in randomised trials such that the impact of this novel class can be adequately assessed in terms of survival and cure rates.

Taxoids represent a new class of agents having both novel chemical structure and mechanism of action. Paclitaxel, a natural product derived from the bark of the Western yew, *Taxus brevifola*, was the first agent of this class to be identified. Extracts of the bark were first examined for antitumour activity in 1962, but it was not until a decade later that Wani[1] described the unique and complex chemical structure of paclitaxel (fig. 1). Interest in the agent grew when Schiff et al. described its novel mechanism of action in 1979.[2] Problems with supply and formulation initially slowed the clinical study of paclitaxel, but by the mid 1980s US National Cancer Institute (NCI) sponsored trials were well under way. At about the same time, the French had produced a number of semisynthetic taxoid derivatives from baccatin III, an extract from the needles of the European yew, *T. baccata*. Docetaxel was the agent selected for further formulation and clinical trials, which were first undertaken in 1990. It differs from paclitaxel in the 10-position on the baccatin ring and in the 3′ position on the side chain (fig. 1).

This review focuses primarily on the comparative clinical pharmacology, toxicity and spectrum of antitumour activity of the taxoids, both of which have recently been approved for use in clinical practice. Brief mention is also made of their comparative preclinical antitumour activity and mechanism of action.

1. Preclinical Data

Tubulin is the cellular target of both paclitaxel and docetaxel.[2,3] In the normal state there exists a dynamic equilibrium between tubulin dimers and microtubules. Energy in the form of guanosine triphosphate (GTP) is required for microtubule formation. In contrast to the vinca alkaloids, another class of tubulin-acting agents, taxoids act to promote tubulin polymerisation and the formation of stable microtubules even in the absence of GTP. The microtubules produced in the presence of taxoids are resistant to disassembly by physiological stimuli and cells exposed to these agents exhibit an accumulation of arrays of disorganised microtubules. This profoundly affects the normal mitotic process and eventually results in cell death.

Although both taxoids bind to the same site on the β-subunit of tubulin,[4] the microtubules produced by each are not identical.[5] Docetaxel produces microtubules of somewhat larger size (an

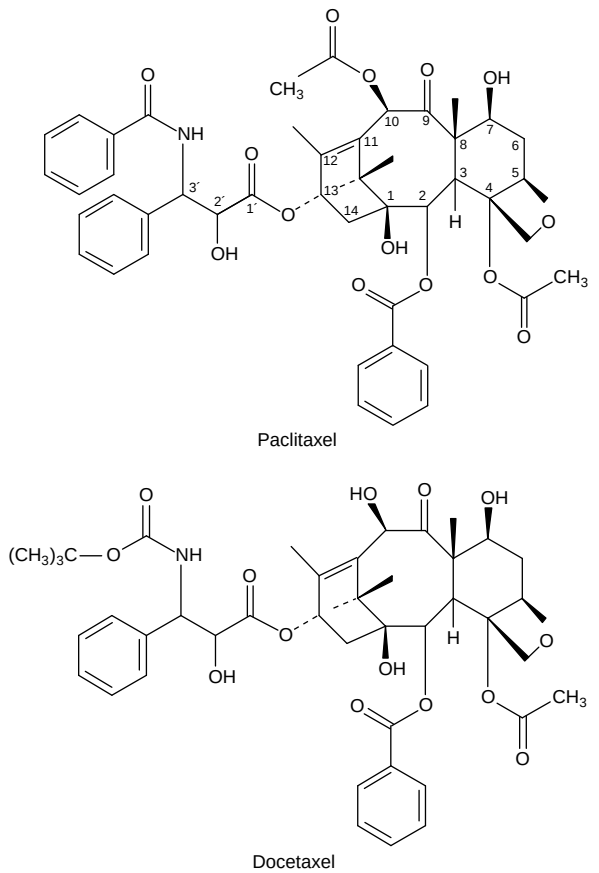

Fig. 1. Chemical structures of paclitaxel and docetaxel.

average of 13.4 tubulin subunits) than paclitaxel (average of 12 tubulin subunits). Furthermore, docetaxel is more avidly taken up by cells and is retained intracellularly for a longer time than is paclitaxel.[6] These features may explain why docetaxel is 2 to 4 times as potent as paclitaxel in *in vitro* and *in vivo* studies of antitumour activity (reviewed in Lavelle et al.[7]). However, both agents show a wide spectrum of activity in an array of murine and human tumour systems[7,8] which led to their selection for clinical development. Several experiments indicated that when the exposure to paclitaxel was prolonged, greater antitumour activity was seen.[8] This observation has fuelled some of the clinical development of the drug as is outlined below.

2. Phase I Clinical Trials

Both taxoid compounds are insoluble in aqueous solutions and thus considerable effort has gone into their formulation. Paclitaxel is formulated in 50% alcohol and 50% cremophor EL, a polyoxyethylated castor oil derivative, and docetaxel is formulated in polysorbate 80 ('Tween 80').

Paclitaxel entered phase I trials in 1983 (table I) and several intravenous regimens were planned.[9-20] However, the appearance of hypersensitivity reactions (HSRs) early in the phase I experi-

Table I. Phase I trials of paclitaxel and docetaxel

Drug	Schedule (infusion duration and frequency)	Premedication	Phase II dose/MTD (mg/m^2)/(mg/m^2)	DLT	Reference
Paclitaxel	1h q 3wk	No	Not recommended	HSR	9
	1h × 1 or × 3 q 3wk	Yes	200 × 1/Not determined	Not seen	10
	3h q 3wk	No	Not recommended	HSR	11
	6h q 3wk	Yes	210/255	Neutropenia	9
	6h q 3wk	Yes	225/275	Neutropenia	12
	6h q 3wk	Yes	280/275	Neutropenia/neuropathy	13
	24h q 3wk	Yes	170/200	Neutropenia	14
	24h q 3wk	Yes	250/275	Neuropathy	15
	24h q 3wk + G-CSF	Yes	250/300	Neuropathy	16
	120h q 3wk	Yes	150/180	Neutropenia/mucositis	17
	1h daily × 5	No	30 × 5/40 × 5	Neutropenia	18
	1h daily × 5	No	Not recommended	HSR	19
	6h daily × 5	Yes	30 × 5/40 × 5	Neutropenia	19
	96h q 3wk	No	140/160	Neutropenia/mucositis	20
Docetaxel	1h q 3wk	No	100/125	Neutropenia/mucositis, nausea	22
	1-2h q 3wk	No	115/100	Neutropenia	23
	1h days 1 and 8	No	50/55	Neutropenia	24
	6h q 3wk	No	80/100	Neutropenia/mucositis	25
	1h daily × 5	No	14 × 5/16 × 5	Neutropenia/mucositis	26
	24h q 3wk	No	70/90	Neutropenia/fever, mucositis	27

Abbreviations: DLT = dose-limiting toxicity; G-CSF = granulocyte-colony-stimulating factor; HSR = hypersensitivity reactions; MTD = maximum tolerated dose.

ence led to 2 important changes to the trials. Infusion duration was extended to 6 or 24 hours and premedication with corticosteroids, and histamine H_1 and H_2 receptor antagonists, was added. These manoeuvres were successful in reducing the incidence of severe HSRs, although minor symptoms such as flushing remained common. It remains a subject of debate whether the taxoid or its vehicle, cremophor, is responsible for the HSR effects.

The initial group of phase I trials found myelosuppression, primarily neutropenia, to be dose-limiting and for phase II evaluation the recommended dose was 135 to 250 mg/m^2 (depending on prior treatment), given as a 24-hour infusion with appropriate premedication. Subsequently, more prolonged schedules (120 hours) and shorter infusions (1-hour, 3-hour), given with premedication, have been studied. Neutropenia has been dose-limiting in most trials but myalgia and neuropathy are also significant dose-related effects with the shorter infusions, and mucositis is more common and severe with prolonged administration. In fact, as was later shown in randomised trials,[21] the neutropenic toxicity of paclitaxel is schedule-dependent: more neutropenia is seen when the same dose is given as a 24-hour infusion than with a 3-hour one. For the most part, phase II and combination studies of paclitaxel have been carried out with one of two schedules of administration: a 24-hour infusion (135 to 250 mg/m^2) or a 3-hour infusion of the same dose, both repeated every 3 weeks.

Docetaxel entered phase I trials in 1990 (table I)[22-27] and, of the several regimens studied, a 1-hour infusion every 3 weeks given at a dose of 100 mg/m^2 was selected for phase II evaluation. Dose-limiting toxicity was neutropenia. Some mucositis and fever were observed but were not as frequent or severe as were noted in repeat administration or long infusion regimens. Because the vehicle in which docetaxel is formulated is different from that of paclitaxel, it was anticipated that HSRs would be less problematic. In fact, the phase I trials drew

to a close without the use of premedication and with only infrequently documented reactions. However, in phase II trials HSRs requiring infusion interruption were noted more often and docetaxel is now given with premedication to ameliorate their severity.

Gratifyingly, both agents demonstrated evidence of antitumour activity in the course of phase I evaluation. Responses were seen in ovarian cancer, melanoma and non–small-cell lung cancer (NSCLC) in the paclitaxel studies and in breast, ovarian cancer and NSCLC in docetaxel studies. Much of the phase II development focused on these same tumour types.

3. Toxic Effects

Phase I trials and data from phase II studies established that both taxoid compounds share many of the same toxic effects including myelosuppression (neutropenia), alopecia, mild gastrointestinal effects and HSR (table II). Whether the latter are a result of the vehicles in which the drugs are prepared or an effect of this class of compound remains unclear. As noted above, neutropenia limits the dose for both drugs and, in the case of paclitaxel, this effect is schedule-related, with longer infusions producing more neutropenia than short infusions. In contrast, even a 1-hour infusion of docetaxel can produce severe neutropenia. This difference may be related to the differing intracellular retention and characteristics of the microtubule formation described above (section 1). Stomatitis can be seen with both agents, although it is most common when prolonged administration schedules are used.

Skin toxicity consisting of erythema, dryness and/or maculopapular rash have been seen in up to two-thirds of patients treated with docetaxel. The nails of those undergoing repeated cycles of treatment may show progressive thickening, discolouration and even loss in some individuals. Although skin rash has occasionally been reported with paclitaxel, it is not common. A syndrome of cumulative fluid retention is also an effect unique to docetaxel. This is manifested by the gradual appearance of peripheral oedema or effusions (which may be confused with tumour progression) with repeated courses of therapy so that approximately half the patients are affected when the cumulative dose reaches 400 mg/m^2. The pathophysiology is not understood but in one randomised study, comedication with oral corticosteroid before and for a few days after treatment delayed the onset of oedema and decreased its severity.[28]

Paclitaxel also has some relatively characteristic adverse effects. Cardiac conduction disturbances, usually manifested as asymptomatic bradycardia, are common. Rarely, more serious disturbances are seen and the presence of a preexisting cardiac conduction abnormality may be a relative contraindication to paclitaxel administration. In a phase I trial of the combination of doxorubicin plus a 3-hour infusion of paclitaxel, a greater than expected incidence of congestive heart failure has been seen; thus, studies of paclitaxel with other cardiotoxic agents should be undertaken with caution.[29] In contrast, single-agent docetaxel has not been shown to produce cardiac effects. More details on the cardiac effects of the combination of an anthracycline and a taxoid are to be found in the section on breast cancer trials (section 5.1).

A dose-related syndrome of myalgia/arthralgia is common after paclitaxel administration but is

Table II. Toxicity of taxoids in recommended dosages

Adverse effect	Paclitaxel		Docetaxel
	3h	24h	1h
Neutropenia	+	++	++
HSR	+	+	+
Hair loss	++	++	++
Mucositis	–	+	+
Cardiac arrhythmia	+	+	–
Arthralgia/myalgia	+	+	–
Neurosensory	+[a]	+[a]	+/–
Cumulative oedema	–	–	+
Skin/nail	–	–	+

a Dose-related and also more prominent when paclitaxel is given over 3h.

Abbreviations and symbols: HSR = hypersensitivity reactions; – = absent; +/– = mild; + = moderate; ++ = severe.

not a feature of docetaxel treatment. Neurosensory symptoms are also frequently noted with paclitaxel although they are usually not severe until high doses are given (e.g. >250 mg/m^2).[30] These effects have also been reported with docetaxel but are not a prominent toxicity at the usual dose and schedule.[31]

4. Clinical Pharmacology

4.1 Pharmacokinetics

Both paclitaxel and docetaxel have undergone extensive pharmacokinetic evaluation. The pharmacokinetic parameters of both drugs given in recommended doses are summarised in table III. Although early studies with prolonged infusions of paclitaxel suggested that it had linear pharmacokinetics,[32,33] later studies showed that it followed nonlinear pharmacokinetics due to saturable distribution, metabolism and elimination.[34-36] This nonlinear pharmacokinetic behaviour is especially evident with infusions of shorter duration such as 3 hours. Both nonlinearity and schedule dependence have their impact on the pharmacokinetic/pharmacodynamic interactions. Pharmacodynamic analyses have strongly indicated that there is a relationship between the percentage decrease in white blood cells (WBC) or absolute neutrophil count (ANC) and the time for which the plasma paclitaxel concentration is above a threshold level of 0.1 μmol/L (or 0.05 μmol/L).[34,36] Others have reported a relationship between the area under the plasma concentration-time curve (AUC) of paclitaxel and the percentage decrease in WBC,[37] and also a rough correlation between neurotoxicity and AUC.[12,35]

In contrast to paclitaxel, the pharmacokinetics of docetaxel are linear, with clearance independent of the administered dose and with plasma AUC increasing in proportion to dose.[23] Both *in vitro* and *in vivo* cytotoxic effects of docetaxel appear to be time- and concentration-dependent. Information on the pharmacokinetics of docetaxel given by more prolonged administration has been scant,[38] since when given in this manner it was associated with more mucosal toxicity and studies were not pursued after phase I. A relationship has been observed between the AUC of docetaxel and the percentage decrease in ANC in patients with solid tumours.[26] This indicates that pharmacokinetic and pharmacodynamic relationships of this drug may also be important in future dosage strategies. Therefore, limited sampling strategies have been developed for both docetaxel and paclitaxel which may greatly accelerate the pharmacokinetic/pharmacodynamic relationships of these agents in large populations.[38-40] It is to be hoped that these studies will shed some light not only on the relationship between toxicity and plasma drug concentrations but also on that between antitumour effect and pharmacokinetic data, in particular the AUC, and duration of drug exposure.

Some indication of the existence of this latter relationship was seen in a study in previously untreated NSCLC patients treated with carboplatin and a 3-hour infusion of paclitaxel.[44] Patients in whom the time above a threshold plasma paclitaxel concentration of 0.1μmol/L exceeded 15 hours survived significantly longer (median 8.2 months) than those who were above this concentration for

Table III. Mean pharmacokinetic parameters of paclitaxel (175 mg/m^2, 3h infusion) and docetaxel (100 mg/m^2, 1h infusion)

Parameter	Paclitaxel[33,34,41]	Docetaxel[3,42,43]
$t_{½\alpha}$ (min)	16	4
$t_{½\beta}$ (min)	140	36
$t_{½\gamma}$ (h)	18.75	11.2
CL (L/h/m^2)	12.69	21
C_{max} (μmol/L)	4.27	4.7
AUC (μmol/L • h)	16.81	5.69
V_{ss} (L/m^2)	99.25	67.3
Protein binding (%)[a]	>95	>95
48h urinary excretion (% dose)	<10	<10
48h fecal excretion (% dose)	≈70	≈70

a Major plasma proteins involved are α_1-acid glycoprotein (AAG), albumin and lipoproteins.

Abbreviations: AUC = area under the plasma concentration-time curve; CL = total body clearance; C_{max} = peak plasma concentration; $t_{½\alpha}$, $t_{½\beta}$ = distribution phase half-lives; $t_{½\gamma}$ = terminal plasma half-life; V_{ss} = volume of distribution at steady-state.

less than 15 hours (median 4.8 months). Further work in this area is needed.

4.2 Metabolism

The major pathway of elimination of both paclitaxel and docetaxel is hepatic metabolism followed by biliary excretion. Although the cytochrome P450 enzyme systems play a pivotal role in the metabolism of both drugs, their metabolic disposition is different. Paclitaxel undergoes hydroxylation at the C6 and the C3′-*para* position leading to the formation of 3 major metabolites: 6α-hydroxy-paclitaxel, 3′-*p*-hydroxy-paclitaxel and 6α,3′-*p*-hydroxy-paclitaxel.[44] Docetaxel has the same positions available for hydroxylation, but it does not occur. The 4 major metabolites of docetaxel are produced by successive oxidation (to alcohol, aldehyde and then acid) of the tert-butyl ester group on the side-chain.[43] The metabolites of both paclitaxel and docetaxel are either inactive or much less cytotoxic than the parent compounds.

From the above it can be foreseen that the concomitant use of drugs which may have inducing or inhibiting effects on these hepatic enzyme systems have the potential to alter the metabolism of paclitaxel or docetaxel. Moreover, it can be expected that patients with impaired liver function will suffer from enhanced toxicity due to changes in metabolism and elimination. Indeed, several studies using different infusion regimens (96-, 24- and 3-hour infusions) have confirmed this (summarised in Nannan Panday et al.[46]). Venook et al.[47] studied a 24-hour infusion of paclitaxel and recommended a dose of 135 mg/m^2 when aspartate aminotransferase (AST) was more than twice the upper limit of normal (ULN) and bilirubin was ≤1.5 mg/dl; a dose of 75 mg/m^2 when bilirubin was 1.6 to 3.0 mg/dl; and 50 mg/m^2 when bilirubin was >3.1 mg/dl. Huizing et al.[48] evaluated a 3-hour infusion of paclitaxel in 3 cohorts of patients with differing levels of liver dysfunction. They concluded that patients with mild to moderate dysfunction (transaminases <10× ULN and bilirubin ≤1.25× ULN), limited prior chemotherapy, and/or age <65 years could safely be given 175 mg/m^2 over 3 hours. No firm conclusion was drawn for patients with more severe degrees of hepatic dysfunction because of limited patient numbers.

In the population pharmacokinetic analyses performed in phase II trials of docetaxel, patients with moderate liver impairment [AST, alanine aminotransferase (ALT) >1.5× ULN and alkaline phosphatase >2.5× ULN] had a 27% decrease in the clearance and a 38% increase in the AUC of docetaxel.[43,49] The recommended dose for such patients is 75 mg/m^2 over 1 hour. For patients with increased bilirubin or ALT/AST of >3.5× ULN, and alkaline phosphatase >6× ULN, no safe dose has as yet been recommended.

4.3 Drug-Drug Interactions

The hydroxylation of paclitaxel to 6α-hydroxy-paclitaxel and 3′-*p*-hydroxy-paclitaxel is catalysed by the cytochrome P450 (CYP)2C8 and CYP3A4 isoenzymes, respectively. For the biotransformation of docetaxel in humans, the CYP3A enzyme subgroup plays a major role. Nonantineoplastic drugs which are specific substrates of these enzymes may therefore have an impact on the pharmacological profile, the toxicity and antitumour effect of the taxoids.[33,46,50] Furthermore, other antineoplastic agents may have interactions with the taxoids when drugs are combined in the clinic.

In fact, sequence-dependent toxicity has been shown for combinations of paclitaxel given over 24 hours or longer with cisplatin, cyclophosphamide and doxorubicin.[51-54] The observed increased toxicity with one of the two sequences correlated with a change in pharmacokinetics.[51,55] In the sequence finding study of cisplatin and paclitaxel, more profound neutropenia was observed when cisplatin preceded paclitaxel. This increased toxicity was related to a 25% decrease in paclitaxel clearance compared with that when the agents were given in reverse order. Interestingly, in contrast to the findings of the combination of doxorubicin and paclitaxel given by prolonged infusion where the sequence of paclitaxel first/doxorubicin second was most toxic, the tolerability of bolus doxorubicin/3-hour paclitaxel was not af-

fected by the order of administration.[29] However, as noted above, the latter combination showed an increased incidence of cardiotoxicity.

Very recent data have shown that 3-hour paclitaxel, in a dose-dependent manner, is responsible for nonlinearity of doxorubicin disposition and elevated plasma concentrations of both doxorubicin and doxorubicinol when the agents are given simultaneously.[56] The effect on plasma doxorubicin exposure is reduced when the agents are given 24 hours apart. The nonlinearity of doxorubicin disposition was also dependent on the concentration of that drug. These effects may have been caused by competition of the 2 drugs for biliary excretion mediated by P-glycoprotein, which is also affected by the paclitaxel vehicle, cremophor EL. These observations illustrate that new paclitaxel-based combinations should be studied with extreme caution when pharmacological interactions are uncertain or unclear.

In patients with solid tumours, the pharmacokinetic parameters of docetaxel and cisplatin were not significantly influenced by their order of administration (cisplatin first or docetaxel first).[57] However, the levels of cisplatin-DNA adducts measured in peripheral WBCs were significantly lower when docetaxel was administered first rather than second.[58] Whether this has any clinical implications remains unclear.

Finally, as yet unpublished data of a phase I study of the combination of docetaxel and ifosfamide revealed that docetaxel has an important influence on the AUC of the latter. When docetaxel precedes a 24-hour infusion of ifosfamide, the clearance of that drug is increased and the AUC reduced significantly in comparison with the reverse sequence of administration (D. Schrijvers, personal communication).

5. Clinical Antitumour Activity

Numerous studies evaluating the single-agent activity of both taxoids have now been completed with reproducible activity noted in breast, ovarian, lung and several other tumour types. For each tumour type the single-agent activity is described below, and comparative remarks are made when appropriate. Finally, data from combination regimens and comments about the role of the taxoids in standard therapy are discussed.

5.1 Breast

Both paclitaxel and docetaxel are active single agents in metastatic breast cancer and, importantly, both have shown evidence of activity in anthracycline-pretreated patients (table IV). Paclitaxel was first reported by Holmes and her colleagues in 1991 to have a response rate of 56% in 25 women with metastatic disease, 14 of whom had received prior treatment for metastases.[59] Since then there have been numerous single-agent studies[20,60-70] of paclitaxel in the treatment of patients with breast cancer. Because these trials enrolled mixed populations of patients in terms of their prior treatment status and employed a variety of doses and regimens of paclitaxel, results have varied considerably. In general, response rates have been higher in patients for whom paclitaxel was first-line metastatic therapy (response rates from 32 to 62%) than in those receiving this treatment as second line or thereafter (response rates from 21 to 48%). Debate about the 'optimal' dose and regimen of paclitaxel administration has not been resolved.

Preclinical data showing that longer exposure yielded superior results and clinical data from nonrandomised trials suggesting higher efficacy with longer infusion have led to 2 randomised studies in metastatic breast cancer patients. The first of these compared a 3-hour to a 24-hour infusion at a dose of 175 mg/m^2.[67] Results did not show an advantage to the longer infusion in terms of response rate (29 *vs* 32%) but survival was longer in the 24-hour arm (9.8 *vs* 13.4 months; $p = 0.02$). As expected, myelosuppression was also more prominent in the longer infusion arm. On the basis of favourable response rates in phase II trials, the second study, a randomised comparison of a 96-hour infusion[20,69] with a 3-hour infusion, is under way. Even if longer infusions prove to be slightly more effective than the 3-hour schedule, the myelosuppression seen with these regimens may limit their use in combi-

Table IV. Single agent trials of paclitaxel and docetaxel in breast cancer

Reference	Prior chemotherapy for metastases (no. of prior regimens)	Dose (mg/m^2)	Schedule (h)	CR/PR	No. of evaluable pts	Response rate (%)
Paclitaxel						
Holmes et al.[59]	0-1	250	24	3/11	25	56
Reichman et al.[60]	0	250 + G-CSF	24	3/13	26	62
Swain et al.[61]	0	135	24	2/4	19	32
Davidson et al.[62]	0	225	3	0/13	25	52
Gianni et al.[63]	0-1 (all pts)	175-225	3	7/12	50	38
	0	175-225	3	11	24	46
	1 (anthracycline)	175-225	3	8	26	31
Seidman et al.[64]	0; ≥2 (all pts)	175/250	3	1/12	49	26
	0	250	3	1/7	25	32
	≥2 (anthracycline)	175	3	0/5	24	21
Fountzilas et al.[65]	0-2 (all pts)	175	3	2/12	33	42
	0	175	3	1/5	11	55
	1-2 (anthracycline)	175	3	1/7	22	36
Nabholtz et al.[66]	0-1	135	3	5/46	227	22
(randomised)	0-1	175	3	12/53	223	29
Peretz et al.[67]	0-1	175	3	N/A		29
(randomised)	0-1	175	24	N/A		32
Seidman et al.[68]	≥1 (anthracycline)	200-250 + G-CSF	24	2/36	76	33
Seidman et al.[69]	1-2 (short taxoid)	120-140	96	0/7	26	27
Abrams et al.[70]	≥2	135-175	24	4/36	172	23
Wilson et al.[20]	≥1 (doxorubicin or mitoxantrone)	140	96	0/16	33	48
Docetaxel						
Hudis et al.[71]	0	100	1	2/18	37	54
Trudeau et al.[72]	0	100	1	3/17	32	63
		75	1	1/5	15	40
Chevallier et al.[73]	0	100	1	5/16	31	68
Dieras et al.[74]	0	75	1	5/12	34	50
Fumoleau et al.[75]	0	100	1	2/23	37	68
ten Bokkel Huinink et al.[76]	1 (8 pts 0)	100	1	2/15	32	53
Adachi et al.[77]	0	60	1	3/14	30	57
	≥1 (28 pts anthracycline)	60	1	2/13	42	36
Valero et al.[78]	≥1 (anthracycline)	100	1	0/18	34	53
Ravdin et al.[79]	≥1 (anthracycline)	100	1	3/17	35	57
Guastalla et al.[80]	≥1 (anthracycline)	100	1	0/15	51	29

Abbreviations: CR = complete response; G-CSF = granulocyte-colony-stimulating factor; N/A = not available; PR = partial response; pts = patients.

nation trials. Ultimately, it is likely that the clinical situation in which paclitaxel is employed (palliative *vs* curative; single agent *vs* combination) will determine the optimal infusion duration.

In addition to comparative trials exploring infusion duration, paclitaxel has also been evaluated in a randomised study of 2 different doses in metastatic breast cancer.[66] In this trial, 471 patients given paclitaxel as a 3-hour infusion were randomly assigned to receive either 135 or 175 mg/m^2. Response rates were observed to be slightly higher in the higher-dose arm (29 *vs* 22%)

but the differences were not statistically significant. A longer time to progression (TTP) was also noted in the higher dose arm (4.2 *vs* 3.0 months; p = 0.027) but survival was similar in both arms. These results are similar to the findings in ovarian cancer[21] and suggest a slight dose-response relationship with this agent.

Phase II studies in breast cancer were an early priority for the development of docetaxel because of activity seen in heavily pretreated cases in some of the phase I trials. In 5 trials docetaxel was given as first-line treatment for recurrent disease[71-75] and one further study[77] included a substantial subgroup of such patients. The majority of studies administered docetaxel in a dose of 100 mg/m^2, but 3 trials included patients treated at lower doses.[72,74,77] Overall response rates in this favourable patient group ranged from 50 to 68%. In trials in which patients had received prior chemotherapy,[76-80] response rates were somewhat lower (29 to 57%) but particular notice has been taken of the apparently high activity in 'anthracycline-refractory' patients where in 3 trials response rates ranging from 29 to 57% were noted.[77-80]

Not yet resolved with respect to the single-agent use of docetaxel in breast cancer is its optimal dose. The dose of 100 mg/m^2 which has been utilised in most studies produces severe myelosuppression in the majority of patients, with a relatively high frequency of febrile complications. This observation, plus the knowledge that certain of the toxic effects of the agent are related to total cumulative dose, have led some to consider that lower doses, if equally effective, would be more appropriate. Non-randomised information on this question is limited: results from the small subset of patients in the trial by Trudeau et al.[72] and the study by Dieras et al.,[74] in which untreated patients received 75 mg/m^2, suggest less activity (response rates 40 and 50%) than other first-line studies. However, in the trial reported by Adachi et al.,[77] where all patients received only 60 mg/m^2 of docetaxel, the response rate in the no-prior-treatment group was 57%. An ongoing randomised trial comparing the doses of 75 and 100 mg/m^2 will address the question directly.

Given that both agents are active in this disease, what comments are possible about their relative merits? The single agent data show that response rates are overlapping, although those for docetaxel have been, in general, somewhat higher than those reported for paclitaxel when categories by prior treatment are considered. However, some of the docetaxel studies have been of small sample size in single institutions, factors which can lead to better results. Clearly, a direct comparison will be necessary to draw firm conclusions and one such trial is ongoing, comparing docetaxel 100 mg/m^2 over 1 hour against paclitaxel 175 mg/m^2 over 3 hours in anthracycline-resistant metastatic breast cancer. The weakness of this design lies in the fact that there are certain to be substantial toxicity differences between the 2 arms: the paclitaxel dose and infusion schedule are known to be associated with little neutropenia, whereas the docetaxel arm will result in grade 4 neutropenia in most patients. If the results indicate greater activity for docetaxel, it will be argued that the arms were not equitoxic. If the results in terms of efficacy are similar, the higher toxicity on the docetaxel arm will allow the conclusion that the therapeutic index for paclitaxel, in this palliative setting, might be greater.

Two randomised trials comparing single agent taxoid with doxorubicin were reported recently, at the May 1997 meeting of the American Society of Clinical Oncology. The first study, by Piccart and colleagues, compared paclitaxel 200mg/m^2/3 hours with doxorubicin 75 mg/m^2 as first-line chemotherapy in 331 patients with metastatic breast cancer.[81] Response rates were 25 and 41% for paclitaxel and doxorubicin, respectively (p = 0.004). Progression-free survival was also longer in the doxorubicin arm (4.1 *vs* 7.3 months; p < 0.001). A crossover to the alternative agent was part of the study design, but response rates have not been reported.

In a similar study, Chan et al.[82] described the activity of docetaxel 100 mg/m^2 compared with the same dose of doxorubicin (75 mg/m^2) as first- or

second-line therapy in 326 patients. The overall response rates were: docetaxel 47% (first-line 58%) and doxorubicin 32% (first-line 44%). TTP data were incomplete but tended to favour docetaxel. These 2 trials had a common control arm of doxorubicin given in the same dose and thus have provided an indirect comparison of the 2 agents in the group of first-line patients. As was noted in some of the phase II trials, these data suggest that docetaxel has higher response rates than paclitaxel when the drugs are given in the doses and schedules described. While we await the results of the direct comparison of the 2 taxoids noted above, the observations from these 2 trials of taxoid *vs* doxorubicin may be of help when selecting a taxoid to build into 'curative intent' (e.g. adjuvant) protocols.

While the debate continues over which taxoid is a better choice as a single agent, investigators have moved forward into developing combination regimens. Should the taxoids add to existing drugs the level of activity that single-agent studies suggest, combination response rates in excess of 70% with a substantial complete response (CR) rate might be expected. Regimens with this level of efficacy could have an impact on survival in advanced disease and would be highly desirable to test in an adjuvant setting.

The first paclitaxel combination development was with doxorubicin and trials were initially performed utilising longer (24 or 72h) infusions of paclitaxel.[53,83] As might have been predicted with the toxicity profile of prolonged infusion of paclitaxel, mucositis and severe myelosuppression were noted. In one study, the severity of mucositis was sequence-related: less toxicity was seen if doxorubicin preceded paclitaxel.[53] The 3-hour infusion of paclitaxel has been easier to combine with other drugs, and phase I studies in combination with bolus doxorubicin and with cisplatin (every 2 weeks) have been completed.[29,84] Both of these studies described very high response rates (94 and 72%, respectively). 41% of the patients in the doxorubicin trial had a complete response. However, an unexpectedly high level of cardiac toxicity was seen (6 of 33 women with clinically reversible congestive heart failure).

Subsequently, a second study of paclitaxel given as a 3-hour infusion combined with doxorubicin confirmed both the high response rate (83%; 24% complete) and also the greater than expected incidence of clinical CHF (6 of 30 patients) at cumulative doses of doxorubicin ranging from 329 to 550 mg/m^2.[85] As described above, recent work by Gianni et al.[56] shows there is a pharmacokinetic interaction between doxorubicin and 3-hour paclitaxel giving rise to nonlinearity of plasma doxorubicin disposition and increased concentrations of the anthracycline. This may explain the apparent increase in cardiac effects.

Paclitaxel plus epirubicin has also been studied in combination in a phase I/II trial and shows a high response rate (84%) with seemingly less cardiotoxicity (3 of 50 patients with clinical CHF) than the studies described above.[86] Docetaxel has also been studied in combination with doxorubicin.[87] Early results show considerable activity and no adverse effects on cardiac function. Trials combining epirubicin and docetaxel are ongoing. It is difficult to draw firm comparative conclusions about the cardiac safety of the various taxoid/anthracycline combinations, since all of the above reports are from small, nonrandomised trials. However, it is reasonable to suggest that combinations of anthracyclines and taxoids must proceed with caution, evaluating cardiac function prospectively until the relationships are clear.

At this point there has only been one reported study comparing taxoid-based combinations with other therapy in breast cancer, although several additional trials of this design are ongoing in both metastatic and adjuvant disease settings. Recently, Sledge et al.[88] presented the results of a 3-arm intergroup study comparing doxorubicin 50 mg/m^2 plus paclitaxel 150 mg/m^2/24 hours plus G-CSF *vs* doxorubicin 60 mg/m^2 *vs* paclitaxel 175 mg/m^2/24 hours as first-line chemotherapy in 739 patients with metastatic breast cancer. The response rate on the combination arm was higher than that on either of the doxorubicin or paclitaxel arms (47 *vs* 36 *vs*

34%; p = 0.007 doxorubicin *vs* combination, p = 0.004 paclitaxel *vs* combination, p = 0.84 paclitaxel *vs* doxorubicin), but no significant differences were seen in CR rates (9 *vs* 6 *vs* 3%). Median time to treatment failure was longer on the combination arm (8.0 *vs* 5.9 *vs* 6.0 months). However, the overall survival was similar in all 3 groups, possibly because of crossover between the single-agent arms. Cardiac toxicity on the combination arm was similar to that seen on the doxorubicin-alone arm, in keeping with the phase I/II trial data, suggesting that cardiac effects are not a problem in combination with doxorubicin when paclitaxel is given over 24 hours.

In view of the increased complexity of the combination arm [requiring granulocyte-colony-stimulating factor (G-CSF)], it is debatable whether it should usurp sequential use of the single agents in this palliative setting. Certainly, CR rates were no higher (9 *vs* 6 *vs* 3%) and quality-of-life measures showed no differences in the 3 arms. Until the results of the other combination trials are available there is no 'standard' combination taxoid regimen which can be recommended outside of study protocols. In clinical practice, taxoids should continue to be used as palliative single agent therapy. In fact, the recently reported study of paclitaxel *vs* cyclophosphamide, methotrexate, fluorouracil and prednisone (CMFP) suggests this single agent is as effective as the traditional multidrug regimen in providing palliative therapy.[89] An assessment of the impact that taxoids will have on the survival of women with this disease awaits completion of other ongoing studies in metastatic and, more importantly, adjuvant disease.

5.2 Ovary

One of the first tumour types to be assessed in paclitaxel phase II development was ovarian cancer where response rates to paclitaxel 135 to 250 mg/m^2/24 hours were seen in 20 to 37% of patients with platinum pre-treated disease[90-92] (table V). It was initially lauded as showing exciting activity in platinum-refractory ovarian cancer but the magnitude of effect in that setting is highly dependent on how 'refractory' is defined. In a large European-Canadian trial, only 12% of patients progressing during therapy with platinum compounds responded to paclitaxel.[21] In this same study, the question of the safety of a short infusion and the effect of 2 doses was explored in a randomised factorial design. Three-hour infusion with premedication

Table V. Single agent trials of paclitaxel and docetaxel in platinum pre-treated ovarian cancer

Reference	Dose (mg/m^2)	Schedule (h)	CR/PR	No. of evaluable pts	Response rate (%)
Paclitaxel					
McGuire et al.[90]	110-250	24	1/11	40	37
Einzig et al.[91]	180-250	24	1/5	30	20
Thigpen et al.[92]	170	24	8/8	43	37
Eisenhauer et al.[21] (randomised bifactorial)	135/175	3/24	6/60	382	17 (all pts)
	135	3/24	2/27	195	15
	175	3/24	4/33	187	20
	135/175	3	3/26	182	16
	135/175	24	3/34	200	19
Seewaldt et al.[93]	250	24	6/19	100	25
Gore et al.[94]	135/175	3	2/20	140	16
Docetaxel					
Francis et al.[106]	100	1	0/8	23	35
Piccart et al.[107]	100	1	2/16	76	24

Abbreviations: CR = complete response; PR = partial response; pts = patients.

was found to pose no greater risk of severe HSRs than 24-hour infusion. No difference in response rates was noted between the short and long infusions or between the doses of 135 and 175 mg/m^2, although TTP was slightly longer in the higher dose group. This finding was similar to that of the randomised trial in breast cancer comparing the same 2 doses over 3 hours.[66]

Cisplatin was the first agent to be used with paclitaxel in combination in this disease and it proved feasible although, as with doxorubicin, the severity of toxicity was dependent on the sequence of administration when paclitaxel was given as a 24-hour infusion.[51] The first randomised trial of this combination in the front-line setting was recently published by the Gynecologic Oncology Group (GOG 111).[95] In 410 suboptimally debulked patients, front-line use of paclitaxel 135 mg/m^2 over 24 hours plus cisplatin 75 mg/m^2 was superior to cyclophosphamide 750 mg/m^2 plus the same dose of cisplatin in terms of TTP (median 18 *vs* 13 months) and overall survival (median 38 *vs* 24 months).

A second large study (680 patients), carried out by a collaboration of 4 European and Canadian cooperative groups, was recently reported.[96] The major differences between the design of this trial and that of GOG 111 were the use of a different paclitaxel dose/regimen (175 mg/m^2 over 3 hours with an option to escalate to 200 mg/m^2), the inclusion of both optimally and suboptimally debulked patients, and the availability of paclitaxel as therapy for relapsed disease in the non–paclitaxel-containing arm. In addition, intervention debulking surgery was permitted for those patients who had suboptimal debulking at the time of trial entry. Results of this study reported at the May 1997 meeting of the American Society of Clinical Oncology indicated that, as in the GOG 111 study, there was a significantly prolonged TTP in the paclitaxel arm (median 16.6 *vs* 12 months). Overall survival data are awaited. More neurotoxicity was noted with the 3-hour paclitaxel infusion than had been described with the 24-hour infusion utilised in GOG 111.

A third randomised trial front-line was reported in the same meeting.[97] This trial, GOG 132, again examined suboptimally debulked patients only, randomising them to receive paclitaxel 200 mg/m^2/24 hours *vs* cisplatin 100 mg/m^2 *vs* the combination in the same doses as GOG 111. Response rates and TTP were lowest in the single-agent paclitaxel arm. The cisplatin alone and the combination arms were similar in TTP and overall survival was similar in the 3 arms. The high proportion of early crossovers in both the single-agent arms made time-to-event analyses difficult to interpret. The paclitaxel plus cisplatin arm had the best combination of efficacy and toxicity of the three and was recommended by the authors. On the basis of these 3 trials, paclitaxel and cisplatin combination therapy can be considered a standard regimen in the first-line treatment of ovarian cancer.

Carboplatin has also been combined with paclitaxel in several studies[98-100] in this disease and in lung cancer patients.[101] Interestingly, less myelosuppression, especially thrombocytopenia, has been noted with this combination than would have been predicted.[102] Randomised trials of the carboplatin/paclitaxel combination *vs* cisplatin/paclitaxel as first-line ovarian cancer treatment are nearing completion. An early report on one such study suggested similar efficacy with more myelosuppression and less neurotoxicity in the carboplatin arm.[103] However, the numbers of patients in the trial were small, so it was underpowered to detect important efficacy differences. The final results of this and the other carboplatin studies are awaited before firm conclusions can be made. Finally, intraperitoneal (IP) treatment with paclitaxel has been studied[104] since this agent has a striking pharmacological advantage when administered by this route compared with the intravenous route. Pilot regimens combining IP paclitaxel with other IP agents or with systemic therapy are ongoing, as are studies combining anthracycline, platinum and paclitaxel.[105]

Comparatively speaking, relatively few studies of docetaxel have been completed in ovarian cancer (table V). In platinum-pretreated patients

docetaxel 100 mg/m^2 produces activity similar to that of paclitaxel (response rate overall 26% in 99 assessable patients).[106,107] Regimens are being developed combining docetaxel with other active agents but, at the time of this writing, no randomised studies of docetaxel in the front-line setting are ongoing.

Of the 2 agents, it is likely that paclitaxel will continue to play a dominant role in the treatment of ovarian cancer because the bulk of the information and the only trials in front-line disease have utilised this taxoid.

5.3 Lung Cancer

5.3.1 Non–Small-Cell Lung Cancer

Initial phase II trials of paclitaxel in NSCLC employed the highest tolerable doses of the agent (200 to 250 mg/m^2) given over 24 hours.[108,109] Response rates with this approach were 21% and 24% in previously untreated patients but neutropenia was severe. Subsequently, doses from 135 to 225 mg/m^2 over 1 to 3 hours have been studied[10,110-112] in a similar population and activity maintained response rate activity in the range of 25% (table VI) with less myelosuppression. The

Table VI. Single agent trials of paclitaxel and docetaxel in non–small-cell and small-cell lung cancer

Reference	Prior chemotherapy	Dose (mg/m^2)	Schedule (h)	CR/PR	No. of evaluable pts	Response rate (%)
Non–small-cell lung cancer						
Paclitaxel						
Chang et al.[108]	No	250	24	0/5	24	21
Murphy et al.[109]	No	200	24	1/5	25	24
Gatzmeier et al.[110]	No	225	3	0/8	37	22
Sekine et al.[111]	No	210	3	23	60	38
Millward et al.[112]	No	175	3	0/5	51	10
Murphy et al.[113]	Yes	175	24	0/1	35	3
Ruckdeschel et al.[114]	Yes	200-250	24	0/2	14	14
Docetaxel						
Fosella et al.[115]	No	100	1	0/13	39	33
Francis et al.[116]	No	100	1	0/11	29	38
Cerny et al.[117]	No	100	1	1/7	35	23
Burris et al.[118]	No	100	1	0/3	14	21
Miller et al.[119]	No	75	1	0/5	20	25
Kunitoh et al.[120]	No	60	1	0/14	72	19
Fosella et al.[121]	Yes	100	1	0/9	42	21
Burris et al.[118]	Yes	100	1	0/3	15	20
Small-cell lung cancer						
Paclitaxel						
Ettinger et al.[134]	No	250	24	0/11	32	34
Kirschling et al.[135]	No	250 + G-CSF	24	0/15	37	41
Smit et al.[136]	Yes	175	3	0/5	14	36
Docetaxel						
Latreille et al.[137]	No	75	1	0/1	12	8
Smyth et al.[138]	Yes	100	1	0/7	28	25

Abbreviations: CR = complete response; G-CSF = granulocyte-colony-stimulating factor; PR = partial response; pts = patients.

activity of docetaxel in chemotherapy-naive patients is very close to that reported with paclitaxel[115-120] over a range of doses (60 to 100 mg/m^2). Given that both agents show activity in untreated patients, 2 different avenues of investigation have been pursued.

In the first, an assessment of taxoid non–cross-resistance to platinum compounds has been pursued by evaluation of the drugs in second-line treatment of NSCLC. Two studies of paclitaxel have been reported[113,114] and an overall response rate of only 6% seen in a total of 46 patients. In 2 separate studies[118,121] docetaxel gave an overall response rate of 21% in a total of 57 patients. These data suggest that docetaxel has greater activity in previously treated patients and 2 randomised trials are ongoing to explore this further. In one study, docetaxel will be compared with best supportive care, and in the second with other single-agent therapies. These studies will help determine not only if the response rates to docetaxel are higher than either of the strategies mentioned, but whether quality of life and survival are favourably affected. Quality of life will be an important end-point in this setting where all patients are destined to succumb from their disease and where therapy may bring with it significant toxic effects.

The second avenue of investigation has been in the development of taxoid-based combination regimens in NSCLC. Combination work with paclitaxel and cisplatin, a logical combination for lung cancer, had already been undertaken in ovarian cancer,[51] and these regimens were also studied in NSCLC. Paclitaxel has also been combined with carboplatin, ifosfamide and vinorelbine in various studies.[122-125] Finally, because of data suggesting that paclitaxel may be an effective radiation-sensitising agent, combination studies of thoracic radiation with either weekly or 2-weekly paclitaxel have been completed.[126,127]

Thus far, there are 2 reported randomised trials of paclitaxel combination therapy in advanced NSCLC. In the first, a 3-arm trial by the Eastern Cooperative Oncology Group (ECOG), cisplatin plus etoposide was compared with either cisplatin plus paclitaxel 135 mg/m^2/24 hours or cisplatin plus paclitaxel 250 mg/m^2/24 hours with G-CSF support. Results in 560 patients have recently been reported in preliminary form.[128] Response rates on the 3 arms were 12.3, 26 and 31%, respectively. Both paclitaxel arms had higher response rates than the control arm ($p < 0.001$), but there was not a strong dose-response relationship between the 2 paclitaxel arms. Median survival was also greater in the paclitaxel arms (9.6 and 10.1 months *vs* 7.4 months for cisplatin/etoposide) although 1-year survival rates remained about the same.

In the second trial, the European Organisation for Research and Treatment of Cancer (EORTC) Lung Cancer group randomised 251 patients to receive either cisplatin plus teniposide or cisplatin plus paclitaxel 175 mg/m^2/3 hours.[129] Results showed lower toxicity and a higher response rate on the paclitaxel arm but no effect on survival.

Both cisplatin and vinorelbine have been combined with docetaxel in NSCLC trials[130-132] but significant haematological toxicity limiting full-dose docetaxel delivery has been noted in these trials. As with paclitaxel, a combination of docetaxel and radiation has been studied in a phase I trial in locally advanced disease.[133] No randomised trials have been completed of docetaxel-based combinations but, interestingly enough, ECOG is conducting a trial of docetaxel/cisplatin versus paclitaxel/cisplatin. Data from this trial should help determine the best taxoid/cisplatin regimen to select for future study in neoadjuvant and other programmes. A randomised trial comparing carboplatin/paclitaxel with cisplatin/paclitaxel is also being carried out by the same group.

5.3.2 Small-Cell Lung Cancer

Compared with NSCLC, there have been relatively few trials of the taxoids in small-cell lung cancer (table VI). Of the 2 taxoids, the results with paclitaxel are more impressive, consistently showing higher single-agent response rates regardless of prior treatment status.[134-138] Pursuit of paclitaxel-based combinations in both the front-line and recurrent disease settings is certainly warranted.

Table VII. Single-agent trials of paclitaxel and docetaxel in squamous cell carcinoma of the head and neck

Reference	Prior chemotherapy for recurrence	Dose (mg/m^2)	Schedule (h)	CR/PR	No. of evaluable pts	Response rate (%)
Paclitaxel						
Forastiere et al.[139]	0	250 + G-CSF	24	2/10	28	43
Thornton et al.[140]	0	250 + G-CSF	24	2/4	23	26
Gebbia et al.[141]	0-1	175	3	0/4	20	20
Docetaxel						
Catimel et al.[142]	0	100	1	2/10	37	32
Dreyfuss et al.[143]	0	100	1	4/9	29	45
Couteau et al.[144]	0	100	1	0/3	11	27
Ebihara et al.[145]	NA	60	1	0/7	19	37

Abbreviations: CR = complete response; NA = not available; PR = partial response; pts = patients.

5.4 Head and Neck

Both paclitaxel and docetaxel have shown moderate levels of single-agent activity in squamous cell cancers of the head and neck[139-145] (table VII).

In 2 studies using a dose of 250 mg/m^2 over 24 hours with G-CSF support in a relatively favourable patient group, including those with untreated locally advanced disease, the overall response rate to paclitaxel was 35%.[139,140] Unfortunately, response duration was short (3 to 5 months) and toxicity was substantial. Early deaths were reported in both trials, several as a result of sepsis. A dose of paclitaxel 175 mg/m^2 over 3 hours without growth factor support given to a less favourable group of patients produced a 20% response rate but was much better tolerated.[141] In contrast to the higher-dose 24-hour infusion trials, no febrile neutropenia was seen. This differential toxicity effect has also been documented in the interim report of a randomised EORTC study of paclitaxel 175 mg/m^2 over 3 or 24 hours *vs* methotrexate in head and neck cancer.[146] In the 24-hour arm there was more grade 4 neutropenia (63 *vs* 5%) and more febrile neutropenia (42 *vs* 0%). No comparative data on response rates are as yet available. However, this trial may lead to a specific recommendation on the most appropriate paclitaxel regimen for palliative therapy. As is the case in other tumour types, the 96-hour infusion regimen is also being studied, but no data are available.

All of the reported docetaxel studies have been carried out with a 1-hour infusion and a dose of either 100 mg/m^2 (3 trials) or 60 mg/m^2 (1 trial). The overall response rate with the higher dose was 36%.[142-144] An update of the Japanese study using a dose of 60 mg/m^2 showed a similar response rate of 37%,[145] in contrast to an earlier report of the same trial where only 12% of patients were apparently responders.[147] Toxicity in these trials was similar to that in other trials of docetaxel given in these doses.

As a result of the activity seen in single-agent studies, taxoid based combination chemotherapy regimens have been studied in several situations: as therapy in patients with recurrent or metastatic disease; as a neoadjuvant treatment in those with locally advanced disease; together with radiation therapy (chemoradiation) and in organ preservation trials. Randomised trial data are available only for paclitaxel (see below) and no clinical data are available for the combination of docetaxel and radiation.

Since preclinical studies demonstrated synergistic cytotoxicity of paclitaxel plus cisplatin,[148] many trials have focused on the combination of a taxoid and a platinum compound. In recurrent disease, the ECOG recently reported the results of a randomised trial of cisplatin 75 mg/m^2 with either high dose (200 mg/m^2/24 hours) or low dose

(135 mg/m^2/24 hours) paclitaxel. Response rates were similar in the 2 arms (34 *vs* 35%), as was the survival experience (median approximately 7 months).[149]

Response rates are higher in the neoadjuvant setting in locally advanced disease. A phase I/II trial of escalating paclitaxel plus cisplatin and G-CSF support documented a 72% response rate.[150] The combination of docetaxel plus cisplatin in a mixed group of neoadjuvant and untreated metastatic disease patients yielded a response rate of 78% (11% with CR).[151] The most spectacular level of activity has been seen in a combination trial of docetaxel, cisplatin, fluorouracil and calcium folinate (leucovorin) in patients with curable, locally advanced squamous cell cancer of the head and neck.[152] All 17 patients treated to date have responded with an overall CR rate of 67% (100% CR rate at primary site). However, even with G-CSF support, toxicity was formidable (febrile neutropenia, mucositis, renal tubular concentration defect). The EORTC is planning a study in patients with locally advanced head and neck cancer comparing this regimen without the use of calcium folinate (CFT regimen) *vs* the 'standard' therapy of cisplatin/fluorouracil. A feasibility study of the CFT regimen is ongoing.

Until randomised results of combination regimens are available, taxoids should be considered primarily as palliative single agents in this disease.

5.5 Miscellaneous Tumours

In addition to the 4 tumour types highlighted above, phase II evaluation of one or both taxoids has taken place in 11 other solid tumours and 2 haematological malignancies. Details of the trials are shown in table VIII.

Little to no activity is reported in phase II trials of docetaxel in renal cell carcinoma[153,154] and colorectal cancer;[155,156] no studies of paclitaxel in these tumours have been published. Single-agent response rates from 10 to 20% have been seen with both agents in melanoma[157-161] and carcinoma of the cervix.[162-164] A similar level of activity has been noted in malignant glioma in 2 trials of paclitaxel.[165,166] However, docetaxel was inactive in the one reported glioma study.[167] Although the response rates are modest, because of the laboratory data mentioned above (section 5.3.1) showing that paclitaxel is a radiation sensitiser, trials combining this agent with radiation have been undertaken in both malignant glioma[168] and carcinoma of the cervix. There was some initial enthusiasm that docetaxel might prove to be an important new agent in soft tissue sarcoma because a European group reported a 17% response rate in patients who had failed previous chemotherapy.[169] However, only an 11% response rate in untreated patients with the disease was documented in a second trial and the level of interest in pursuing the drug in this tumour has waned.[170] Paclitaxel showed only a 4% response rate in the single reported study in soft tissue sarcoma.[171]

Several taxoid studies have been reported in previously untreated patients with upper gastrointestinal tract malignancies, with mixed results. Ajani et al.[172] gave 50 patients, with chemotherapy-naive oesophageal cancer, treatment with paclitaxel 250 mg/m^2/24 hours and documented one complete and 15 partial responses for an overall response rate of 32%. Activity was seen in both squamous and adenocarcinoma histologies. On the other hand, using the same dose and schedule of paclitaxel, Einzig et al.[173] reported only one response in 22 patients (5%) with untreated adenocarcinomas of the upper GI tract. In the same group of patients, docetaxel gave a 14% response rate in one study and in a second trial (gastric carcinomas only) 24% of patients responded.[174,175]

More substantial antitumour activity has been seen in urothelial carcinomas, germ cell tumours and endometrial cancer. Paclitaxel had response rates of 42 and 56% in 2 trials in untreated patients with recurrent urothelial cancers (primarily bladder).[176,177] Docetaxel has also shown activity in the disease but there are fewer data available. In a trial in cisplatin-refractory patients, docetaxel 100 mg/m^2 produced a 20% response rate.[178] Toxicity in that trial was high, with 11/20 patients developing febrile neutropenia. No trials utilising a lower

Table VIII. Results obtained from therapy with paclitaxel and docetaxel in other solid tumours

Tumour	Agent	Reference	No. of prior chemotherapy regimens[a]	Dose (mg/m^2)	Schedule (h)	CR/PR	No. of evaluable pts	Response rate (%)
Renal	Docetaxel	Bruntsch et al.[153]	0	100	1	0/1	27	4
		Mertens et al.[154]	0	100	1	0/0	18	0
Colorectal	Docetaxel	Pazdur et al.[155]	0	100	1	0/0	19	0
		Sternberg et al.[156]	0	100	1	1/2	33	9
Melanoma	Paclitaxel	Legha et al.[157]	0	250	24	0/3	25	12
		Einzig et al.[158]	0	250	24	3/1	28	14
	Docetaxel	Bedikian et al.[159]	0	100	1	1/4	40	13
		Aamdal et al.[160]	0	100	1	0/5	30	17
		Einzig et al.[161]	0	100	1	1/0	13	8
Cervical	Paclitaxel	McGuire et al.[162]	0	170	24	2/7	52	17
		Kudelka et al.[163]	0	250 + G-CSF	3	0/5	22	23
	Docetaxel	Kudelka et al.[164]	0	100	1	0/2	16	13
Glioma	Paclitaxel	Prados et al.[165]	0-1[b]	210-140	3	0/4	40	10
		Chamberlain & Kormanink[166]	1[b]	175	3	0/4	20	20
	Docetaxel	Forsyth et al.[167]	0	100	1	0/0	18	0
Soft tissue sarcoma	Paclitaxel	Waltzman et al.[171]	0-1	250	3	0/1	27	4
	Docetaxel	van Hoesal et al.[169]	1	100	1	0/5	25	17
		Blackstein et al.[170]	0	100	1	0/3	28	11
Upper GI tract	Paclitaxel	Ajani et al.[172]	0	250	24	1/15	50	32
		Einzig et al.[173]	0	250	24	10/1	22	5
	Docetaxel	Einzig et al.[174]	0	100	1	1/2	22	14
		Sulkes et al.[175]	0	100	1	0/8	33	24
Urothelial	Paclitaxel	Roth et al.[176]	0	250 + G-CSF	24	7/4	26	42
		Dreicer et al.[177]	0-2	175-250	24	0/5	9	56
	Docetaxel	McCaffrey et al.[178]	1 (CDDP)	100	1	0/4	20	20
Germ cell	Paclitaxel	Christou et al.[179]	≤ 3	170	24	1/1	18	11
		Bokemeyer et al.[180]	2	225	3	1/5	24	25
		Motzer et al.[181]	1-2	250 + G-CSF	24	3/5	31	26
Endometrial	Paclitaxel	Thigpen et al.[182]	0	250	24	4/6	28	35
		Woo et al.[183]	1 (CDDP)	170	3	0/3	7	43
Non-Hodgkin's lymphoma	Paclitaxel	Wilson et al.[184]	1-8	140	96	0/5	29	17
		Younes et al.[185]	1-5	200	3	6/6	53	23
		Younes et al.[186]	1-8 (+ paclitaxel 3h)	140	96	0/0	12	0
		Goss et al.[187]	1-6	175	3	0/2	15	13
Myeloma	Paclitaxel	Dimopoulos et al.[188]	0	125 135	24 3	0/5	33	15

a For recurrent disease.

b Chemotherapy after radiation or for recurrence.

Abbreviations: CDDP = cisplatin; CR = complete response; G-CSF = granulocyte-colony-stimulating factor; GI = gastrointestinal; PR = partial response; pts = patients.

dose of docetaxel in this malignancy have been reported but such a study should be undertaken.

In germ cell tumours (primarily testicular cancer) 3 trials of paclitaxel have been reported.[179-181] Docetaxel is being studied in this setting but no data are available as yet. The paclitaxel studies are of interest since they included only patients failing after 1 to 3 curative intent chemotherapy programmes (in some, high dose chemotherapy with autologous stem cell support). In the 73 patients enrolled in the trials there were 4 complete and 11 partial responses. Although these data do not mean that single-agent paclitaxel represents effective salvage therapy, it does indicate that the agent is active and approaches to incorporate it into earlier treatment in high risk patients seem warranted. Both 3-hour and 24-hour infusion schedules were studied with no obvious difference in outcome. The 3-hour schedule might be advantageous to pursue since it can be more easily combined in full dose with other myelosuppressive agents.

In endometrial cancer, 2 studies of paclitaxel have been reported but none utilising docetaxel. While data are limited, those available suggest this tumour is also very sensitive to paclitaxel. The GOG reported a 35% response rate in 28 previously untreated patients who received paclitaxel 250 mg/m^2 over 24 hours.[182] In a small series of 7 patients with platinum-refractory endometrial cancer, Woo et al.[183] reported 3 responses to paclitaxel 170 mg/m^2 over 3 hours. The GOG is now conducting a phase I trial to determine safe doses of a cisplatin, paclitaxel and doxorubicin combination to study in a randomised trial in recurrent endometrial cancer.

Little information has been published on the activity of taxoids in haematological malignancies, and that which is available, is for paclitaxel.[184-188] Wilson et al.[184] reported a 17% response rate to 96-hour infusion paclitaxel in very heavily pretreated patients with non-Hodgkin's lymphoma. Although they speculated that the long infusion was relevant to the activity in this very drug-resistant population, the observation by Younes et al.[185] of a 23% response rate in a similarly heavily pretreated population given a 3-hour infusion of paclitaxel makes it more likely that the agent itself is the determinant of activity, not the duration of infusion. Younes and colleagues[186] also studied the efficacy of a 96-hour infusion in patients who had failed to respond to a 3-hour exposure to the drug: no responses were seen. In untreated myeloma, a low response rate of 15% has been reported in one study. Paclitaxel merits further evaluation in non-Hodgkin's lymphoma, probably first in second-line combination salvage regimens.

6. Conclusions

The taxoids are very similar in their preclinical activity, mechanism of action and spectrum of clinical activity. Both are myelosuppressive agents, but for paclitaxel this effect is schedule-related, with shorter infusions producing less myeloid toxicity. This observation has fuelled an ongoing debate about the optimal schedule (3 *vs* 24 hours) of paclitaxel with the proponents of short infusions citing as advantageous the ease of administration and combination regimen development and those in favour of long infusions citing preclinical data relating efficacy to longer exposure. In most palliative and many adjuvant regimens, the shorter paclitaxel infusion is in use.

Regimen-related myelosuppression is not noted with docetaxel and all clinical development of this agent has been carried out with a 1-hour administration.

Some subtle differences in the intracellular retention of docetaxel compared with paclitaxel may account for the lack of schedule-related myelosuppression of docetaxel and its greater potency, and may also be relevant to the skin toxicity and oedema which are seen with long term docetaxel administration. Information about the drug-drug interactions of these agents, in relation to their individual degrees of hepatic metabolism, remains only modest at this point but will be important to pursue since early data suggest that the 2 drugs may differ in anthracycline combinations with respect to cardiac toxicity.

Since paclitaxel has been clinically investigated longer than docetaxel, in general, more mature clinical trial data are available for this paclitaxel, including several first-line combination therapy trials in ovarian cancer. Here, paclitaxel in combination with a platinum compound seems to have proven itself as a standard regimen. It is uncertain if docetaxel will be evaluated in this context.

An abundance of clinical data is available for both analogues in breast cancer, although all trials reported to date have been in the advanced, metastatic setting. Both have been compared as single agents with doxorubicin, with the results suggesting paclitaxel in a 3-hour infusion is inferior to the anthracycline (in terms of response rate), and those of docetaxel suggesting it is superior to the same dose of doxorubicin. This indirect comparison favours the activity of docetaxel; however, it is clear that in the dose/schedules studied, the taxoid compounds are not equitoxic. A direct comparison in breast cancer is under way, but the results to date would favour the use of docetaxel in designing regimens to evaluate in the adjuvant (curative intent) setting.

For the treatment of metastatic disease, either single agent remains appropriate but lack of cumulative toxicity may make paclitaxel more attractive in some situations where prolonged administration is foreseen. Lung cancer trials have also confirmed the activity of both agents, although docetaxel appears to have slightly more promising activity in previously treated patients than paclitaxel. This patient population is the subject of a randomised trial comparing docetaxel with best supportive care. Paclitaxel in combination with cisplatin has been evaluated in 2 randomised trials in first-line treatment of NSCLC. The results of these trials taken together suggest this combination has an impact on survival similar to other new regimens now considered 'standard' in the front-line setting in this disease.

Unfortunately, despite the plethora of phase II data generated with paclitaxel and docetaxel in numerous other tumour types, there is still much to learn before either drug can be said to fit into the 'standard' management of malignant disease. Additional studies will be required before taxoid based combinations have been evaluated sufficiently in randomised trials to accurately assess their impact in terms of survival and cure rates.

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Correspondence and reprints: Dr *Elizabeth A. Eisenhauer,* NCIC Clinical Trials Group, 82-84 Barrie Street, Queen's University, Kingston, Ontario, Canada K7L 3N6.
E-mail: eisenhae@ncic.ctg.queensu.ca