REVIEW ARTICLE

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Risks and Benefits of Taxanes in Breast and Ovarian Cancer

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Abstract

The taxanes are a unique class of agents with a broad spectrum of clinical activity. They act by binding to tubulin, producing unnaturally stable microtubules and subsequent cell death.

The distribution and elimination of paclitaxel depend on dose and administration rate. This nonlinearity is much less evident at lower infusion rates (24-hour infusions) and more evident at high plasma concentrations (3-hour infusions). The pharmacokinetics of docetaxel also suggest the presence of nonlinear pathways, but these appear to be clinically insignificant at the current doses utilised

(60 to 100 mg/m^2). Both agents undergo hepatic metabolism and biliary excretion and require dose adjustment in the setting of liver dysfunction. Drug interactions are quite common with these agents, some of which are sequence-dependent and clinically significant.

The optimal dose of paclitaxel is not known at this time, and controversy over possible dose- or schedule-related differences in efficacy still remain. Docetaxel is somewhat more consistent in its dose and scheduling information, but controversy remains regarding a dose-benefit relationship as well as scheduling differences (weekly *vs* every 3 weeks).

Toxicity profiles for these agents are somewhat different. Paclitaxel is more likely to be associated with peripheral neuropathy and myalgias/arthralgias than docetaxel. Docetaxel is more likely to be associated with a cumulative fluid retention syndrome that can be dose limiting.

Paclitaxel and docetaxel are both highly active agents against breast cancer, including tumours that are resistant to anthracyclines. Docetaxel tends to have higher response rates overall, but direct comparisons at maximally tolerated doses have not been completed. Combination regimens with many different agents are attempting to improve on the responses seen with single-agent taxanes.

The combination of paclitaxel and a platinum compound should be utilised as first-line therapy of advanced ovarian cancer. Controversy lies in the choice of the platinum compound and the dose and administration schedule of paclitaxel. Substitution of docetaxel for paclitaxel in these platinum-containing regimens is also being investigated. The taxanes also exhibit activity against ovarian cancer in patients previously exposed to platinum agents. These agents may also be administered intraperitoneally for local therapy of metastatic ovarian cancer.

Although docetaxel and paclitaxel are often considered similar in activity and tolerability, this review emphasises the fact that these agents are indeed different. Clinicians need to be familiar with the benefits and adverse events related to each agent in order to make informed, appropriate clinical decisions.

In the 1960s the National Cancer Institute initiated a massive search for natural compounds with antineoplastic activity. From this process, a new class of drugs emerged with outstanding preclinical efficacy; however, many obstacles would have to be overcome before these agents would enter into clinical investigations. The first agent to be identified, paclitaxel, was found to have significant *in vitro* activity, but was extremely difficult to solubilise for administration and was found in only small quantities in the bark of the pacific yew tree, *Taxus brevifolia*.[1] The mechanism of action of the new agent was not delineated until the late 1970s, when Schiff et al.[2] first described the tubulin-stabilising properties of paclitaxel. Solving these problems would take the next 20 years, but what resulted has significantly impacted the care of many patients with cancer.

Docetaxel was developed in order to circumvent the issues of solubility and availability that faced paclitaxel early in its development and marketing. Docetaxel is slightly more water soluble than paclitaxel; however, both agents require a complex solvent system for solubilisation.[3] Docetaxel is produced semisynthetically from 10-deacetylbaccatin -III, found in the needles of the European yew tree, *Taxus baccata*.[4] This is important because for the first time there was a renewable source for the production of a taxane.

Experiments with paclitaxel, searching for alternative sources, found a similar production process for paclitaxel. Today, paclitaxel is produced through

a semisynthetic process, chemically altering the 10-deacetylbaccatin-III molecule to form paclitaxel in the laboratory.[3] Paclitaxel is also produced by an endophytic fungus associated with *Taxus brevifolia*, *Taxomyces andreanae*.[5] The amount of paclitaxel produced from this organism is small, but genetic engineering may prove to enhance this production. Currently this process is not utilised with commercially available paclitaxel.

Although availability is no longer a problem, issues surrounding solubility are still challenging. The solvent system employed with paclitaxel, Cremophor-EL® and ethanol, consists of a castor oil/ethanol blend commonly used with other commercially available drugs. This solvent system is, at least in part, responsible for hypersensitivity reactions and may affect the metabolism of the drug through inhibition of the cytochrome P450 (CYP) enzyme family.[6] Effects of Cremophor-EL® on the multidrug resistance P-glycoprotein may also alter the antitumour activity of paclitaxel.[7] These facts make changing the solvent system to improve solubility a difficult task, requiring duplication of all clinical data available with the current formulation. This task may not be worth the effort in light of mechanisms developed to overcome obstacles encountered with the use of Cremophor-EL®.

Non-Cremophor formulations of paclitaxel have been developed and are entering clinical trials. These include liposomal,[8,9] pegylated,[10] and polymeric micellar[11,12] formulations of paclitaxel, as well as new water-soluble derivatives[13,14] that may overcome issues of solubility and adverse events associated with solvent systems. Only time will tell whether these new formulations will produce similar efficacy. Oral administration is also being investigated, but is complicated by the presence of the multidrug transporter P-glycoprotein in the intestine.[15] Oral administration of paclitaxel and docetaxel with potential inhibitors of the P-glycoprotein (e.g. cyclosporin) has been attempted,[16-18] but there are minimal data in humans supporting this method of administration as a viable alternative.[17,18] Docetaxel is solubilised in polysorbate-80 and ethanol, which is also associated with infusion-related adverse events, although in the absence of premedication, hypersensitivity reactions occur at a decreased frequency when compared with paclitaxel.[19-23]

This article outlines and compares paclitaxel and docetaxel in their mechanism of action, resistance, pharmacokinetics, dose and administration, adverse events, and clinical activity. Subtle, yet important, differences exist between paclitaxel and docetaxel, requiring an intimate knowledge of both agents when making treatment decisions and dose, administration and management recommendations. This is not intended to be a comprehensive review of every aspect of the taxanes, but should provide the framework upon which to base clinical decisions.

1. Pharmacology

Until Schiff et al.[2] outlined the mechanism of action of paclitaxel in 1979, there was little known about the antineoplastic nature of these compounds. Today, more is understood regarding the mechanism of action of the taxanes; however, there are many aspects yet to be discovered.

Paclitaxel and docetaxel bind to the β subunit of tubulin, producing unnaturally stable microtubules that prevent depolymerisation and cause cell death.[2] The actual mechanisms that lead to cell death remain unclear, but may include activation of several intracellular signal transduction pathways essential for apoptosis.[24,25] Paclitaxel binds to the N-terminal 31 amino acids of β-tubulin and produces abnormal asters, for which centrioles are not necessary.[26-28] Paclitaxel-treated cells are not prevented from traversing from cell cycle stage G_2 into mitosis, but its primary effects occur in late G_2 and early mitosis.[29] Cell death after exposure to paclitaxel appears to involve apoptotic mechanisms, including classic features such as DNA fragmentation, cell volume shrinkage, and membrane-bound apoptotic bodies.[30]

Differences between paclitaxel and docetaxel exist in that docetaxel appears to be twice as potent as paclitaxel, binding to tubulin with greater affinity than paclitaxel.[31] This binding difference appears to contribute to the prolonged intracellular retention[32] of docetaxel and may impart better clinical

outcomes, but this has yet to be clinically proven. The number of protofilaments produced after paclitaxel exposure is 13, compared with 12 seen in normal cells and in cells exposed to docetaxel.[33] This difference may be related to the different side chains at C-13.[34] Microtubules formed after docetaxel exposure differ structurally from those formed after paclitaxel exposure[34,35] and these agents may act during different phases of the cell cycle.[36] In synchronised HeLa cells, docetaxel appears to act preferentially in the S phase and has only partial activity in the G_2/M phase.[36] Paclitaxel, in this same experimental system, appears to have greatest activity during the G_2/M phase of the cell cycle.[29,36] The clinical significance of these findings is unknown. Induction of bcl-2 phosphorylation, facilitating apoptosis, and inhibition of angiogenesis are also considered important functions of the antitumour activity of the taxanes.[37,38] Although these subtle differences in pharmacology probably have little bearing on clinical antitumour activity, they may impart clinical differences regarding pharmacokinetics, dose and administration, and adverse events.

One mechanism of resistance to the taxanes involves the multidrug resistance gene, MDR-1.[39] The overexpression of this gene produces an amplification of membrane P-glycoprotein synthesis. These P-glycoproteins act as efflux pumps and prevent the nuclear action of the taxanes. This appears to be an active mechanism of resistance for both paclitaxel and docetaxel.[39,40] Altered α- and β-tubulin subunits are found in a paclitaxel-resistant cell line (Chinese hamster ovary cells) which also possesses a slow rate of microtubule assembly to compensate for the presence of paclitaxel.[41] This cell system requires paclitaxel for microtubular function. When these cells are exposed to docetaxel, the majority of cells die, demonstrating a difference in resistance patterns between these 2 taxanes. Cells resistant to docetaxel, in 1 experiment, demonstrated decreased levels of β-tubulin messenger RNA compared with parent cells.[40] Alterations in α- or β-tubulin subunits may alter binding of these agents and impart resistance, as mentioned previously. Alterations in the specific types of β-tubulin present may also impart resistance. Kavallaris et al.[42] demonstrated this effect in an epithelial ovarian cancer cell line. Paclitaxel resistance in this cell line was correlated with an increased level of class I, III, and IVa β-tubulin isotypes. Therefore, the types and amounts of tubulin appear to be important in determining sensitivity to the taxanes.

Lack of cross-resistance between the taxanes is also evident clinically. In a study by Valero et al.,[43] docetaxel demonstrated activity in patients resistant to paclitaxel with a response rate of 18% and an even higher response rate of 25% in patients who previously received paclitaxel by short infusions (over 1 or 3 hours). Potency differences could explain these responses. However, these data are still intriguing.

The proto-oncogene HER2/neu (c-erbB2) has recently been implicated in taxane resistance, and the approval of a humanised monoclonal antibody directed against this target, trastuzumab, has allowed for clinical testing of this hypothesis. Controversy surrounding this issue has stemmed from conflicting reports in the literature regarding taxane sensitivity and HER2 overexpression in breast cancer. Retrospective clinical data from Memorial Sloan-Kettering Cancer Center evaluating response to the taxanes (paclitaxel or docetaxel) in patients with metastatic breast cancer indicate increased sensitivity to taxanes when tumours overexpress HER2.[44,45] Other data from the M.D. Anderson Cancer Center laboratories indicate that tumours (breast cancer cell lines) overexpressing HER2 are indeed more resistant to paclitaxel therapy.[46,47] Prospective data from a recent trial of paclitaxel therapy administered to patients with HER2-overexpressing breast cancers illustrates the overall resistance of these tumours to the taxanes. Only a 15% response rate was demonstrated in the paclitaxel arm of the study.[48] Similar clinical data with docetaxel are currently not available. A clinical trial has compared paclitaxel with or without trastuzumab for front-line therapy of HER2-overexpressing metastatic breast cancer. The overall response rate (RR) and median time to progression with the addition of trastuzumab were significantly

greater than with paclitaxel given alone [RR 38 *vs* 15% ($p < 0.001$) and median time to progression 6.7 *vs* 2.5 months ($p < 0.0001$), respectively].[48] However, the 1-year survival rate was not significantly improved [73 *vs* 61% ($p = 0.08$), respectively]. Whether improved response rates with trastuzumab/paclitaxel are attributable to effects on the HER2 signal transduction pathway or simply to other effects on apoptosis or the cell cycle has yet to be determined. Further investigation into this biological interaction is ongoing. Approval of trastuzumab by the US Food and Drug Administration (FDA) for front-line therapy of HER2-overexpressing metastatic breast cancer in combination with paclitaxel was based on this clinical information. Data with docetaxel are forthcoming in similar ongoing trials, but clinical information is not yet available to make comparisons.

2. Pharmacokinetics and Pharmacodynamics

Both paclitaxel and docetaxel are large, multiring structures that are highly insoluble in water and exhibit different pharmacokinetic properties (see table I for specific pharmacokinetic information).[19,49-54] Both agents have large volumes of distribution, are highly protein bound, especially to α_1-acid glycoprotein, distribute to nearly every tissue except the central nervous system, and undergo extensive hepatic metabolism and biliary excretion.

Paclitaxel appears to exhibit saturable distribution and dose-dependent clearance.[53] This saturable distributive phase explains the delay in peak plasma concentrations observed in the perinfusional period. Increasing the paclitaxel dose or administration rate leads to a decrease in plasma clearance, which can be explained by these saturable pathways.[53] The rate of elimination is usually greater than the rate of distribution, and clearance is only greatly reduced when patients are given large doses or short infusions. At higher doses and administration rates, the plasma concentration of paclitaxel begins to exceed the metabolic capacity of the elimination pathways, thereby increasing the area under the plasma-time curve (AUC) disproportionately.[53] Conversely, at low plasma concentrations, such as that seen with 24-hour infusions, the nonlinearity of the pharmacokinetics of paclitaxel is less evident.[54]

Unlike paclitaxel, the pharmacokinetics of docetaxel do not suggest that capacity-limited metabolism plays a role in its disposition.[19-22,52,55,56] Docetaxel pharmacokinetic analyses suggest that at standard doses (60 to 100 mg/m^2) no nonlinearity exists.[56] At these doses, the behaviour of docetaxel can be described using simple linear pharmacokinetic models. At higher doses (115 mg/m^2 or higher), such as those being investigated as part of the preparative regimen for stem cell transplant, nonlinear pharmacokinetics may better explain the disposition of docetaxel.[56] Careful dose escalation is required in these studies, as small increases in dose may produce disproportionate increases in exposure (AUC).

The pharmaceutical vehicle used to solubilise the taxanes may influence the disposition of these agents

Table I. Mean pharmacokinetic parameters of the taxanes

Parameter	Paclitaxel						Docetaxel
	3h[49]	3h[49]	6h[50]	24h[49]	24h[49]	96h[51]	1 or 2h[19,52]
Dose (mg/m^2)	135	175	170-275	135	175	120-160	20-115
$t_{½\alpha}$ (min)	12	16.2	21.6	5.4	8.4		5
$t_{½\beta}$ (h)	1.4	2.3	6.4	2.2	2.0		1
$t_{½\gamma}$ (h)	14.4	18.8		49.8	23.6		13.5
CL (L/h/m^2)	17.6	12.7	11.7	21.8	23.6	27.8	21.0
V_{ss} (L/m^2)	98	99	59	657	269		67.3
C_{max} (μmol/L)	2.5	4.3	2.2-13.0	0.2	0.4	0.063	3.78

CL = systemic clearance; $\mathbf{C_{max}}$ = peak plasma concentration; $\mathbf{t_{½\alpha}}$ = α half-life; $\mathbf{t_{½\beta}}$ = β half-life; $\mathbf{t_{½\gamma}}$ = γ half-life; $\mathbf{V_{ss}}$ = volume of distribution at steady state.

and explain, in part, the difference observed in the clinical pharmacology of these 2 agents. Cremophor-EL®, utilised in the commercial formulation of paclitaxel, may be responsible for the reduction in plasma clearance observed at higher drug doses, contributing to the prominent nonlinearity found with paclitaxel as compared with docetaxel.[57] Controversy exists regarding which method of pharmacokinetic analysis is the best to analyse drugs that possess a third, redistribution, phase (such as the taxanes) and that require prolonged sampling (up to 72 hours) in order to adequately capture data that represent the late (γ) phase of elimination. Compartmental models may not be the best method for analysing these data, and noncompartmental models may better represent this type of elimination.[56] The limiting factor in accurately describing the extended elimination phase for drugs such as paclitaxel is the inadequate sampling interval in most clinical studies. To appropriately determine the clearance of these agents requires extended blood sampling (past 24 hours) seldom found in these types of trials.

Population pharmacokinetics of docetaxel, utilising a 3-compartment model, reveal that plasma clearance of docetaxel is independent of dose, but body surface area, plasma levels of α_1-acid glycoprotein and hepatic function appear to be important predictors of clearance.[52] High levels of α_1-acid glycoprotein are associated with decreased clearance attributable to the binding of docetaxel to this protein, as only unbound drug is available for elimination. However, levels of α_1-acid glycoprotein should not affect the AUC of unbound docetaxel, and clinical consequences related to α_1-acid glycoprotein levels are not expected.[52] High baseline levels of α_1-acid glycoprotein were predictive of poor response and increased risk of relapse in patients with lung and breast cancer, but were also predictive of decreased toxicity in this study.[52] These data are contradictory to the previous statement, clearly demonstrating an incomplete understanding of the clinical consequences surrounding the disposition and binding of docetaxel. α_1-Acid glycoprotein is an acute-phase protein and can be altered in many different physiological and pathological conditions, including cancer. In addition, multiple variants of this protein exist and are dependent on multiple factors, including genetic predisposition. More information is required regarding the interaction of α_1-acid glycoprotein with docetaxel pharmacodynamics and the physiological role of α_1-acid glycoprotein variants.

Clinical measures of hepatic function may be important predictors of clearance.[52] Patients with concomitant elevations of transaminases (ALT or AST >1.5 × upper limit of normal) and alkaline phosphatase (>2.5 × upper limit of normal) had an observed decrease in docetaxel clearance of 27%.[52] This difference is clinically significant and has led to recommendations for dose adjustment in patients with impaired liver function based on the above parameters (see section 3). The recommended premedication regimen of dexamethasone given prior to and during docetaxel administration does not appear to significantly alter the pharmacokinetics of docetaxel.[52]

Both paclitaxel and docetaxel are extensively metabolised by the CYP enzyme family. Different metabolic pathways within the CYP enzyme system degrade the taxanes. Docetaxel is nearly completely metabolised by the CYP3A4 subfamily of isoenzymes.[58] Paclitaxel, in comparison, is metabolised by both the CYP3A4 and CYP2C8 isoenzymes, causing differences in the potential for drug interactions between the 2 agents.[58] Formal drug interaction studies have been performed with numerous agents. With the exclusion of other chemotherapy agents, few of these interactions appear to be clinically significant.

Sequence-dependent interactions with combinations of paclitaxel and cisplatin and paclitaxel and doxorubicin are of interest because of the differing toxicity and efficacy profiles when different sequences are utilised.[59-61] Cisplatin appears to alter the clearance of paclitaxel, worsening toxicities when cisplatin precedes paclitaxel administration.[59] The reverse administration schedule can be given with less neutropenia, and efficacy appears to be similar with both regimens. Paclitaxel and doxorubicin have an opposite effect. Paclitaxel alters the clearance of

doxorubicin, worsening cardiac toxicity, neutropenia and mucositis when paclitaxel precedes doxorubicin.[60,61] This interaction is profound when both agents are given as prolonged infusions.[60] Docetaxel would be expected to also exhibit similar interactions; however, combinations with doxorubicin and cisplatin have not shown this to be the case.[62,63]

In order to better predict clinical responses (therapeutic and toxic), knowledge of the pharmacodynamics of an agent is required for optimal dose selection. The pharmacodynamics of paclitaxel and docetaxel are complex. Many investigators have set out to determine a correlation between response and/or toxicity and pharmacokinetic parameters. For breast and ovarian cancers, an association between any pharmacokinetic parameter and therapeutic response to paclitaxel or docetaxel has yet to be made.

Many investigators have made correlations between toxicities seen with paclitaxel and measures of drug exposure. The duration of time spent with concentrations of paclitaxel above 0.05 to 0.1 μmol/L has been proposed as a predictor of granulocytopenia.[49,51,54,64] Initially, investigators chose the 0.1 μmol/L concentration based on *in vitro* data demonstrating this as the lowest effective concentration resulting in clinically relevant cytotoxicity.[65] Other investigators have established the 0.05 μmol/L plasma concentration as a more pertinent threshold value when comparing the degree of myelosuppression between different infusion schedules. Plasma concentrations of 0.1 μmol/L, which are associated with an increased incidence of granulocytopenia and mucositis, are usually not achieved with prolonged infusions (24 hours) compared with shorter infusions (3 hours).[54] Pharmacological intermediate end-points such are threshold plasma concentrations are only useful if they perform consistently regardless of administration schedule. The time spent over this concentration limit (0.05 μmol/L) has been shown to fulfil these requirements satisfactorily.[54,64] The incidence and severity of neurotoxicity has also been correlated with paclitaxel exposure (AUC). Sonnichsen et al.[53] demonstrated a significant relationship between neurological and musculoskeletal toxicity in children receiving escalating doses of paclitaxel administered over 24 hours. Children who experienced neurological or musculoskeletal toxicity had higher median areas under the curve compared with children who did not experience these toxicities [no toxicity: median AUC 30 μmol/L · h (range 9 to 90 μmol/L · h); neurological toxicity: median AUC 54 μmol/L · h (range 22 to 115 μmol/L · h), p = 0.062; musculoskeletal toxicity: median AUC 71 μmol/L · h (range 15 to 92 μmol/L · h), p = 0.052].[53] Huizing et al.[66] found a similar correlation in their examination of patients receiving 3-hour infusions of paclitaxel. However, other investigators have failed to find any relationship between neuromuscular toxicity and paclitaxel exposure.[64] A variety of dissimilarities in patient populations and pre-existing subclinical neurological conditions make direct correlations in the limited patient populations studied difficult.

Similar data also exist for docetaxel exposure. Investigators have made associations between AUC and granulocytopenia.[21,55] Pazdur et al.[21] examined the relationship between docetaxel AUC on day 1 and the percentage decrease in absolute granulocyte counts in patients receiving docetaxel as a daily infusion for 5 days. Using a sigmoidal maximum effect (E_{max}) model, they demonstrated that the AUC resulting in a 50% decrease in absolute granulocyte counts was 263 μg/L · h.[21] Bisset et al.[55] demonstrated an association between AUC, end of infusion plasma drug concentrations and degree of neutropenia, but failed to find any such correlations between these indices and severity of mucositis.

Although these studies have yielded interesting relationships between taxane disposition, toxicity and efficacy, the clinical utility of these intermediate end-points is questionable. Among the limitations of these studies are the patient populations studied, typically a limited number of heavily pretreated participants with diverse nonresponsive tumour types, with the largest number of patients receiving ineffective drug doses (phase I). The elucidation of clinically useful relationships awaits data derived from large

phase II and phase III trials, incorporating pharmacokinetic studies, in responsive tumour types.

3. Dose and Administration

3.1 Dose and Schedule Selection

Paclitaxel and docetaxel are usually administered intravenously every 3 weeks as either a single agent or in combination with other chemotherapeutic agents. Several different doses and schedules of paclitaxel have been investigated and the optimal administration has yet to be determined. The FDA has approved single agent paclitaxel in a dose range from 135 to 175 mg/m^2 given over 3 or 24 hours.[67] Other administration schedules have been shown to be tolerable with different maximum tolerated doses, including infusions of 1-hour, 6-hour and 96-hour durations.

Prolonged infusions of paclitaxel have been associated with increased response rates in metastatic breast cancer.[51,68,69] However, 1 trial directly comparing a 3-hour and a 96-hour infusion demonstrated no significant improvement in efficacy with the prolonged infusion schedule (RR 23% with 3-hour *vs* 29% with 96-hour infusion; survival 11 *vs* 10 months, respectively).[70] In another trial, paclitaxel 250 mg/m^2 given over 3 hours was compared with the same dose given as a 24-hour infusion. Although a significantly higher response rate was demonstrated with the longer infusion time (50 *vs* 40%, p = 0.001), overall survival and time to progression were no different between the 2 groups.[69] Duration of infusion did not appear to significantly affect the response duration or overall survival seen in patients with ovarian cancer.[49] Prolonged infusions have a slightly different adverse effect profile compared with short infusions and are somewhat inconvenient for patients, requiring bag changes every 48 hours with the current formulation. Trissel et al.[71] have developed an extemporaneously compounded formulation that will allow stability for at least 7 days. This new formulation requires clinical investigation to ensure similar efficacy and tolerability, but could be a convenient strategy for patients to receive prolonged infusions.

Several studies are ongoing investigating schedule-dependent issues related to paclitaxel. The maximum tolerated dose for paclitaxel (without growth factor support) given over 3 hours is 250 mg/m^2,[65] for 24-hour administration 225 mg/m^2,[72] and for 96-hour administration 140 mg/m^2.[51] In a randomised phase III trial comparing paclitaxel at 175 mg/m^2, 210 mg/m^2 or 250 mg/m^2 given over 3 hours in metastatic breast cancer, there appeared to be no significant difference in response rates [21 *vs* 28 *vs* 22% (p = 0.64), respectively] or median survival [9.8 *vs* 11.8 *vs* 11.9 months (p = 0.48), respectively] between these doses.[73] There was a statistical correlation between increasing dose and time to treatment failure (3.8 vs 4.1 vs 4.8 months, p = 0.03). In the metastatic setting, maximum tolerated doses are often not used because of the palliative nature of the treatment. This is a caveat to remember when comparing data across studies and between agents.

Many other administration regimens for paclitaxel are currently being investigated, including weekly and biweekly schedules. The weekly schedule may mimic continuous infusions, increasing cellular exposure to the drug and affecting more cells as they are actively dividing. The maximum tolerated dose for the weekly paclitaxel schedule is 80 to 100 mg/m^2 without growth factor support.[74,75] One report demonstrated the feasibility of 175 mg/m^2 given weekly without growth factor support, but this trial has yet to be confirmed and was associated with a high incidence of neurotoxicity.[76] The weekly paclitaxel schedule nearly eliminates haematological toxicity and allows for greater dose intensity, delivering approximately 50% more drug in the same time period compared with 250 mg/m^2 over 3 hours given every 3 weeks. This is not the case with docetaxel given on a similar schedule.

Comparing dose intensity between regimens is dependent on what is considered the standard dose and schedule and what is the comparator regimen. As mentioned previously, the optimal dose and duration of therapy of paclitaxel are not known, and therefore any comparisons of dose intensity are relative. For example, if it is believed that 225 mg/m^2 every 3 weeks is the standard dose of paclitaxel, ad-

ministering 80 mg/m^2 weekly (240 mg/m^2 per 3 weeks) would not be much of a gain in terms of dose intensity. However, if it is believed that 175 mg/m^2 every 3 weeks is the standard dose of paclitaxel, then 80 mg/m^2 weekly (240 mg/m^2 per 3 weeks) is a substantial benefit in terms of dose-intensity. Another caveat to remember is that the assumption that increased dose intensity will lead to better clinical outcomes has yet to be proven in a prospective clinical trial.

Docetaxel has been recommended for breast cancer at doses ranging from 60 to 100 mg/m^2.[77] The maximum tolerated dose in phase I studies in the US and Europe was 100 mg/m^2,[19,20] and in Japan was 60 mg/m^2.[78] It appears that both dose levels are effective against breast cancer, but indirect comparisons demonstrate that higher doses (100 mg/m^2) are associated with better overall response rates, but substantially more toxicity.[79] A trial comparing 60 mg/m^2, 75 mg/m^2 and 100 mg/m^2 given over 1 hour is ongoing. Recommendations regarding starting doses should take into account organ function, prior chemotherapy exposure and performance status of the patient.[80] Docetaxel administered daily for 5 days and prolonged infusions have shown an increase in toxicity without adding to the overall efficacy of the agent.[21,22,55] These data are from phase I studies investigating 24-hour infusions,[55] short infusions daily × 5,[21] and weekly administration (days 1 and 8).[22] Weekly administration has resurfaced as a potential schedule because of information regarding dose intensity of the taxanes in breast cancer. A maximum tolerated dose of 43 mg/m^2 was determined when docetaxel was given on a continuous weekly schedule, but the recommended dose for phase II trials was 36 mg/m^2.[81] The dose-limiting toxicity does not appear to be neutropenia with this schedule, but rather fatigue and asthenia. As mentioned previously for paclitaxel, the goal of increased dose intensity is not greatly improved with this schedule of docetaxel. At the most, a 15% increase in dose intensity can be achieved compared with the 3-week schedule more commonly utilised, but these comparisons are relative in light of the lack of consensus regarding the optimal dose.

Paclitaxel and docetaxel require dose reductions in patients with mild to moderate liver dysfunction and should not be given outside the context of a clinical trial in severe liver dysfunction (total bilirubin >1.5 times the upper limit of normal). Data regarding this issue are sparse and consist of only a single study for each agent. Venook et al.[82] prospectively studied paclitaxel in patients with differing degrees of liver dysfunction in a phase I clinical trial. Patients were divided into 3 cohorts determined by the degree of liver dysfunction exhibited (see table II). Although the peak serum concentrations of paclitaxel in these patients were not different from those in historical control patients with normal liver function, the time that serum concentrations were above 0.05 μmol/L appeared to be prolonged in patients with liver dysfunction and this occurrence appeared to correlate with more se-

Table II. Guidelines for administration of taxanes to patients with liver dysfunction. The investigators emphasised the need to calculate doses according to the individual clinical situation

Study	Drug	Liver function parameters			Recommended dose (mg/m^2)
		AST/ALT	AP	total bilirubin (mg/dl)	
Venook et al.[82]	Paclitaxel	AST: 2 x ULN	NA	<1.5	Unknown[a]
		Any	NA	1.6-3.0	100[b]
		Any	NA	>3.0	75[b]
Bruno et al.[52]	Docetaxel	>1.5-3 x ULN	>2.5 x ULN	<1.25 x ULN	75[c]

a For this cohort of patients, the data are insufficient to determine a safe starting dose for a 3-hour infusion.

b For 3-hour infusion.

c Or 25% reduction, assuming standard doses of 60-100 mg/m^2.[52]

AP = alkaline phosphatase; **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **NA** = not available; **ULN** = upper limit of normal.

vere adverse events, especially neutropenia. It appears from these data that short infusions are preferred in this patient population, secondary to delayed clearance of paclitaxel; however, the number of patients treated in the 3-hour cohort was too small to draw any sound conclusions.[82] Bruno et al.[52] assessed the population pharmacokinetics and pharmacodynamics of docetaxel in patients with both normal and abnormal liver function. Patients with liver dysfunction included in the trials were only mildly affected, with total bilirubin levels of 1.5 × the upper limit of normal or less. In their assessment, the authors found a 27% decrease in clearance of docetaxel in patients with moderately elevated hepatic enzymes and essentially normal total serum bilirubin levels. This decrease in clearance did correlate with an increased risk of toxicity. Dose recommendations for paclitaxel and docetaxel in patients with liver dysfunction are listed in table II. Administration of these agents to patients with severe liver dysfunction should not be done outside the context of a clinical trial.

In combination regimens, the taxanes are generally utilised in lower doses because of the additive toxicity experienced with combination regimens. This, of course, depends on what is considered 'full dose'. Docetaxel is generally administered at 60 to 70 mg/m^2 and paclitaxel at 175 to 200 mg/m^2 when given in combination regimens. Relatively speaking, the dose of paclitaxel given in combination regimens is usually closer to full dose when compared with docetaxel. Some of the more promising combinations with paclitaxel include doxorubicin, vinorelbine, fluorouracil, cisplatin and carboplatin. Some agents being investigated with docetaxel include doxorubicin, cisplatin, carboplatin, fluorouracil, cyclophosphamide and gemcitabine, to name a few.

3.2 Premedication Guidelines

Administration of paclitaxel requires premedication with both H_1- and H_2-antagonists and corticosteroids to prevent hypersensitivity reactions; see table III for premedication guidelines.[67] The H_2-antagonists utilised in this manner include cimetidine 300mg, ranitidine 50mg and famotidine 20mg. Intravenous administration of diphenhydramine 50mg, famotidine 20mg and dexamethasone 20mg at 30 minutes prior to paclitaxel administration appears to be efficacious on the basis of a recently published report.[83] Current product information[67] warns that all patients should be premedicated, although there is evidence to suggest that prolonged infusions of paclitaxel (96 hours or longer) do not require premedication.[51,68,70,84]

The premedication regimen for docetaxel consists of only oral dexamethasone.[77] Although one goal of premedicating before docetaxel is to prevent hypersensitivity reactions, the major reason corticosteroids are used in this regimen is to delay the onset and decrease the severity of fluid reten-

Table III. Premedication guidelines for the taxanes

Premedication	Paclitaxel				Docetaxel
	1h	3h	24h	96h[a]	1h
H_1-antagonist (diphenhydramine 50mg)	IV prior	IV prior	IV prior	None	None
H_2-antagonist (cimetidine 300mg, ranitidine 50mg, famotidine 20mg)	IV prior	IV prior	IV prior	None	None
Dexamethasone	PO 20mg 12 and 6h prior[b]	PO 20mg 12 and 6h prior[b]	PO 20mg 12 and 6h priorb	None	PO 8mg bid × 3 days beginning 24h prior

a Treatment guidelines recommend that all patients receiving paclitaxel be premedicated with corticosteroids, diphenhydramine and h2 antagonists; however, there is evidence to suggest that such premedication may not be necessary with prolonged infusions of paclitaxel (96 hours or longer).

b Intravenous dexamethasone 20mg has been shown to be effective given just prior to administration of paclitaxel.[83]

bid = twice daily; **IV** = intravenous; **PO** = orally.

tion and decrease the severity and incidence of skin and nail changes associated with docetaxel administration. The manufacturer initially recommended a 5-day regimen of dexamethasone 8mg orally twice a day, beginning 24 hours prior to docetaxel administration. There are now data indicating that the 3-day regimen appears to have a similar rate of fluid retention and less mucositis and infection associated with its use.[85] This has led the manufacturer to change its recommendation for premedication to a 3-day regimen of dexamethasone, consisting of only 6 doses (dexamethasone 8mg twice daily for 3 days beginning 24 hours before administration).[77]

Existing controversy over premedication regimens with the weekly taxane schedules has led investigators to use an abbreviated schedule of dexamethasone with weekly docetaxel (8mg orally 12 and 1 hour prior to administration and 12 hours after administration for a total of 3 doses),[81] which should help decrease the risk of infections. Prolonged weekly administration of high dose corticosteroids in the cancer population should be avoided, as the risk of infectious complications may be increased with these administration schedules. Similar concerns exist with paclitaxel as well. There are ongoing trials investigating other methods of prevention of hypersensitivity reactions with weekly paclitaxel, but the only method for prevention of fluid retention secondary to docetaxel has been the corticosteroid schedule mentioned previously (3 days). Ongoing research into this problem is necessary in order to make educated decisions regarding the premedication regimens required for weekly administration of the taxanes.

4. Adverse Events

4.1 Haematological

The dose-limiting toxicity of both paclitaxel and docetaxel is neutropenia or, more specifically, febrile neutropenia. Paclitaxel at 250 mg/m^2 given over 24 hours has a 16 to 36% incidence of febrile neutropenia.[86,87] At this dose, most investigators advocate colony-stimulating factor support given prophylactically with the first course. However, the administration of paclitaxel at this dose level with growth factor support is associated with an 18% incidence of febrile neutropenia (a level greater than that seen with shorter infusion schedules).[69] When given as a shorter infusion (1- or 3-hour), paclitaxel 250 mg/m^2 is associated with a significantly lower incidence of febrile neutropenia (≤5%),[69,88,89] not warranting the prophylactic use of colony-stimulating factors according to the American Society of Clinical Oncology's guidelines for use of colony-stimulating factors.[90] When given as a prolonged infusion (e.g. 140 mg/m^2 over 96 hours), the incidence of severe (grade 4) neutropenia appears to be approximately double that seen with the 3-hour infusion.[88] However, the incidence of febrile neutropenia is similar between the 2 schedules. The severity of neutropenia is dependent on the number of prior chemotherapy regimens a patient has received and generally is higher in patients with metastatic disease.

It is difficult to compare rates of febrile neutropenia between paclitaxel and docetaxel because of the diverse patient populations, doses, and administration schedules utilised in each study.[69,78,87,91] Caution should be used when making such comparisons in the clinical decision-making process. Weekly administration of paclitaxel appears to be well tolerated, with minimal myelosuppression, peripheral neuropathy and arthralgia/myalgia syndrome associated with this administration schedule.[74,75]

Docetaxel has a high incidence of grade 4 neutropenia; however, the incidence of febrile neutropenia appears to be lower (generally less than 25%) than that seen with paclitaxel given as a 24-hour infusion.[79] However, the incidence of febrile neutropenia seen in phase II studies has been as high as 51% with a docetaxel dosage of 100 mg/m^2 in patients with prior exposure to anthracycline-containing regimens[80] and as low as 2% with a dosage of 75 mg/m^2 as front-line therapy for metastatic disease.[92] The use of colony-stimulating factors 'up front' with the 100 mg/m^2 dosage is controversial because of the rate of febrile neutropenia, but could be argued as a reasonable option for minimising toxicity and maximising dose intensity. Data

utilising prophylactic oral quinolones has demonstrated a decrease in the incidence of infections in patients with solid tumours receiving chemotherapy.[93] This approach may also be effective in circumventing hospital admissions for infection and/or febrile neutropenic episodes encountered with either paclitaxel or docetaxel.

With paclitaxel, the neutropenia is not cumulative and the white blood cell counts begin to fall approximately 5 to 7 days after administration and reach a nadir between days 7 to 14, with nearly every patient recovering by day 21.[33] Docetaxel is associated with an early drop in white blood cell counts, beginning as early as day 4 to 6 and reaching the lowest level at day 6 to 8.[78] As with paclitaxel, nearly every patient has recovered by day 21 of therapy and the neutropenia is not cumulative with repeated courses of therapy.[78] Thrombocytopenia and anaemia are not commonly experienced with paclitaxel and docetaxel, but mild cases have been reported.[33,78] The weekly schedule of docetaxel has demonstrated a lack of neutropenic events and may be better tolerated because of this fact alone.[81]

4.2 Neuromuscular

Cumulative peripheral neuropathy is seen with paclitaxel, exhibiting a stocking-glove distribution and manifesting as a sensory neuropathy progressing to motor loss with continued administration.[33] The severity and incidence appear to be related to the length of the infusion, with shorter infusions being associated with a higher incidence of severe neuropathies. This means that with shorter infusions, peripheral neuropathies occur much earlier in therapy and are more severe. Myalgias and/or arthralgias are seen beginning approximately 48 to 72 hours after administration with an expected duration of 48 to 72 hours.[33] These effects also appear to be related to the length of infusion, with shorter infusions being associated with more severe myalgias/arthralgias. In a study comparing 3-hour infusions of 175, 210 and 250 mg/m^2 of paclitaxel, the incidence of myalgias and neuropathy was higher at the 210 (13%) and 250 mg/m^2 (26%) dose levels compared with the 175 mg/m^2 dose level (6%).[73] Prolonged infusions of 96 hours have been associated with less peripheral neuropathy and myalgias compared with shorter infusion schedules.[70] Prolonged infusions may be better suited for patients who are unable to tolerate the peripheral neuropathy and myalgias/arthralgias associated with shorter infusions. Peripheral neuropathy and myalgias/arthralgias are also seen with docetaxel, but to a lesser degree and are generally not limiting factors for continued treatment.[78]

4.3 Fatigue

Asthenia and fatigue are seen quite frequently with both paclitaxel and docetaxel (4 to 15% and 34 to 73%, respectively).[81,87,88,94] This is often categorised with the myalgias and arthralgias commonly seen with paclitaxel and is difficult to distinguish as a separate entity. For this reason, many of the trials with paclitaxel did not identify this as a significant issue. Also, patients in the early trials with paclitaxel were generally more heavily pretreated and had multiple sites of metastases, factors that may contribute to fatigue. Fatigue appears to be dose limiting for the weekly schedule of docetaxel.[81] Asthenia is usually mild to moderate with docetaxel, with approximately 20% of patients experiencing severe asthenia when the 3-week schedule is utilised.[94]

4.4 Skin and Hair

Total body alopecia is seen with both paclitaxel and docetaxel and occurs approximately 10 to 14 days after therapy begins.[33,78] Skin and nail changes are seen with both agents and consist of dry skin, nail ridging, and onycholysis with paclitaxel[33] and palmar/plantar erythrodysaesthesias (hand-foot syndrome), scattered macular/papular rash, vein tracking (with peripheral administration), nail ridging and onycholysis with docetaxel.[78] This type of reaction is more commonly associated with docetaxel. However, skin and nail changes are more frequently encountered with the introduction of weekly paclitaxel. Both taxanes are currently classified as irritants, but, if extravasated, have rarely been associated with ulceration.[95] Care should be

taken when administering either taxane through a peripheral intravenous site and, if extravasated, the application of ice to the site after aspiration has been attempted is recommended.[77] No specific antidotes have been identified to assist with management of extravasations of the taxanes.

4.5 Oedema

Fluid retention syndrome appears to be unique to docetaxel; however, a small number of patients receiving paclitaxel have reported mild peripheral oedema in the trials to date. Fluid retention is a cumulative phenomenon and appears at an average cumulative dose of 400 mg/m^2 when docetaxel is given without corticosteroid premedication.[96] With the addition of dexamethasone premedication, the incidence of severe oedema was decreased from 20% without premedication to 6.3% with a 5-day corticosteroid-based premedication regimen.[97] The first sign of fluid retention is bodyweight gain and should be closely monitored with each course of therapy. Early treatment with diuretics appears to be effective in limiting the severity of this toxicity. If docetaxel is continued and the fluid retention is not treated, progression to pleural and/or pericardial effusions and ascites may occur.[78] Patients with congestive heart failure or other comorbid conditions require particularly close monitoring for this adverse effect, recognising that small increases in fluid volume may lead to exacerbation of symptoms.

4.6 Hypersensitivity Reactions

Hypersensitivity reactions are seen with both paclitaxel and docetaxel. They range from a mild rash to severe anaphylactic reactions. Often they are associated with hypotension. They are believed to be caused by the vehicles in which the drugs are solubilised; however, a contribution of the drugs themselves should not be discounted. Prolonging infusions and adding premedication with corticosteroids, H_1- and H_2-antagonists has helped to decrease the incidence of this adverse effect to less than 3% with paclitaxel.[33] Since docetaxel has a lower incidence of hypersensitivity reactions associated with its administration, use of dexamethasone alone has been adequate in preventing the majority of these reactions. Close monitoring for the first 30 to 60 minutes of the infusion has been shown to be adequate, as most reactions occur within the first 10 minutes of the infusion.[98] These agents are usually administered in an outpatient setting and anaphylactic kits or emergency supply carts should be readily available near the infusion area. If a patient has an allergic reaction to paclitaxel, rechallenge has been accomplished successfully, employing a more rigorous premedication regimen and/or slowing the infusion rate;[99] however, this method of rechallenge has also failed in some patients.[100]

4.7 Cardiovascular

Asymptomatic bradycardia is the most common cardiac manifestation of paclitaxel toxicity and is estimated to occur in approximately 30% of patients.[101] More severe bradyarrhythmias and heart block have also been reported, but occur less frequently. Secondary to these effects, patients with a history of cardiac rhythm disturbances or patients on medication that may predispose them to these effects should be monitored closely. Hypotension during the infusion has been reported with paclitaxel and may be related to the Cremophor-EL® rather than to paclitaxel itself. Cardiac toxicity has not been evident with docetaxel. There have been scattered reports of arrhythmias in patients receiving docetaxel, but the causative relationship with docetaxel has not been determined to date.[77] In phase I trials, patients were assessed with Holter monitors for 24 hours after administration of docetaxel and did not exhibit any dysrhythmias during this period.[21,22]

4.8 Gastrointestinal

Gastrointestinal effects of the taxoids are generally minimal and include mild nausea, mucositis, diarrhoea and elevations in liver function tests. Standard premedication regimens do not include separate antiemetics, because of the low emetogenic potential of these agents. Dexamethasone is a

very effective antiemetic and may help to prevent any potential nausea caused by the taxanes; however, as with any chemotherapeutic agent, it is wise to give the patient antiemetics as needed while at home. Prolonged infusions of paclitaxel and docetaxel are associated with more mucositis and diarrhoea.[55,70] There have been a few reports of neutropenic enterocolitis (typhlitis) after paclitaxel[102-104] or docetaxel[105] administration when given in high doses or in combination with doxorubicin or cyclophosphamide.

5. Clinical Activity

5.1 Metastatic Breast Cancer

Paclitaxel and docetaxel are highly active agents against breast cancer. To date, both agents have an established role in the treatment of metastatic disease. Paclitaxel is approved by the FDA for use in breast cancer at 175 mg/m^2 given over 3 or 24 hours; however, the maximum tolerated dose is much higher (250 mg/m^2 over 3 hours). As was outlined previously, direct comparison of 175 mg/m^2, 210 mg/m^2 and 250 mg/m^2 of paclitaxel has shown no significant difference in response rates or overall survival in patients with metastatic breast cancer.[73] Response rates with paclitaxel in patients with metastatic disease range from 21 to 62%.[51,106-108] Patients included in early trials were heavily pretreated with and without prior anthracyclines, and doses and administration were variable. In anthracycline-resistant breast cancer, response rates approach 50% when paclitaxel is given over 96 hours,[51] but range from 21 to 36% when given over 3 hours and 33% when given over 24 hours.[109] Anthracycline resistance is often defined differently in individual studies; therefore, it is important to recognise the criteria for determining resistance when reviewing and comparing these data.

Paclitaxel 200 mg/m^2 over 3 hours has been compared with CMFP (cyclophosphamide, methotrexate, fluorouracil, prednisone) in patients with untreated metastatic breast cancer.[91] In a preliminary report of the first 100 patients enrolled, the investigators noted similar response rates between the regimens [RR 31%, 95% confidence interval (CI) 19 to 45% *vs* 36%, 95% CI 22 to 51%, respectively], but found a significant advantage of improved quality of life for patients receiving paclitaxel compared with deteriorating quality of life with the CMFP regimen.[91] Median time to progression was longer with CMFP (6.4 months *vs* 5.5 months), but median survival was higher with paclitaxel (16.5 months *vs* 11.3 months). These values were not compared statistically. The small number of patients analysed in this preliminary report limits the power of these observations. Nonetheless, paclitaxel appears to be as active as CMFP and may be better tolerated on the basis of the quality-of-life data.

Doxorubicin is still considered one of the most active agents against breast cancer and has also been compared with paclitaxel as a single agent. In this randomised clinical trial, paclitaxel 200 mg/m^2 over 3 hours was compared with doxorubicin 75 mg/m^2 as first-line therapy for patients with anthracycline-naive metastatic breast cancer.[110] Crossover to the other agent was required upon disease progression within the first 7 cycles of chemotherapy, but was optional if progression occurred after that point in time. Response rates and median progression-free survival were significantly better with doxorubicin (RR 41%, p = 0.004; median progression-free survival 7.3 months, p = 0.0001) compared with paclitaxel (RR 25%; median progression-free survival 4.0 months). These results were surprising and somewhat controversial because of the dose and schedule of paclitaxel utilised in this trial.

In a 3-arm trial conducted under the auspices of the Eastern Cooperative Oncology Group, doxorubicin 60 mg/m^2 as a bolus was directly compared with paclitaxel 175 mg/m^2 over 24 hours; combination of the 2 agents (doxorubicin 50 mg/m^2 and paclitaxel 150 mg/m^2 over 24 hours) comprised the third arm of the study.[111] Response rates were similar (p = 0.84) between the doxorubicin (RR 34%) and the paclitaxel (RR 33%) arms of the study. Median time to treatment failure and median overall survival were not significantly different between the 2 single-agent arms of the study (median time to treat-

ment failure 6.2 months *vs* 5.9 months, p = 0.68; median overall survival 20.1 months *vs* 22.2 months, p = NS; doxorubicin *vs* paclitaxel, respectively). Patients on the single-agent arms of this study were crossed over to the other agent upon progression, which limits the ability to detect differences in overall survival. However, according to the available data, paclitaxel and doxorubicin appear to have similar antitumour activity. Responses were seen in patients who crossed over from doxorubicin to paclitaxel (20%) and vice versa (14%). Gastrointestinal toxicity associated with paclitaxel was less severe, making the acute phase of therapy easier to tolerate. Cardiac toxicity was less problematic with paclitaxel, making it attractive for use in early stage disease where the majority of patients will live long enough for long term toxicities to become apparent.

In a phase II randomised study of paclitaxel compared with mitomycin, patients with metastatic breast cancer were randomised to receive paclitaxel 175 mg/m^2 as a 3-hour infusion every 3 weeks or mitomycin 12 mg/m^2 as a slow bolus infusion every 6 weeks.[112] Response rates were higher in the paclitaxel group (17 *vs* 6%, p = 0.14), but statistical significance was not reached. Median time to progression was significantly prolonged with paclitaxel compared with mitomycin (3.5 versus 1.6 months, respectively; p = 0.026). The median survival in the paclitaxel arm appeared to be longer than with mitomycin, but this difference was not statistically significant. Patients progressing while on mitomycin were crossed over to paclitaxel; out of 21 patients, 5 partial responses (24%) were seen. These data demonstrate that paclitaxel maintains efficacy even in the setting of multiple prior therapies.

Docetaxel also has very good activity against breast cancer. In previously untreated patients, response rates range from 40 to 68%, better than any other single agent chemotherapy.[79,96] Anthracycline resistance usually poses a problem for most patients with breast cancer and implies a poor prognosis. Docetaxel, in 1 trial, demonstrated a 57% response rate in patients with breast cancer with anthracycline-resistant tumours.[94] This excellent response rate was confirmed in another trial by Valero et al.[83] in a similar patient population (RR 53%). Median time to progression in these trials was similar to that seen with other second-line therapies in metastatic breast cancer (5 months and 7.5 months, respectively). In a randomised trial of docetaxel 100 mg/m^2 over 1 hour compared with mitomycin plus vinblastine, patients with anthracycline-resistant metastatic breast cancer demonstrated significantly better response rates (30 *vs* 11.6%, p < 0.0001), time to progression (19 *vs* 11 weeks, p = 0.001) and overall survival (11.4 *vs* 8.7 months, p = 0.0097) with single agent docetaxel compared with the combination regimen.[113]

Another combination compared with docetaxel 100 mg/m^2 over 1 hour was sequential methotrexate (200 mg/m^2 on day 1) with fluorouracil (600 mg/m^2 on days 1 and 8) administered to patients with advanced anthracycline-resistant breast cancer.[114] Preliminary results from this phase III trial indicate that docetaxel appears to be more active than the sequential combination of methotrexate and fluorouracil. Response rates (42 *vs* 19%, p < 0.001) and median time to progression (6 *vs* 3 months, p = 0.006) were significantly better in the docetaxel arm, again demonstrating that docetaxel is effective therapy against anthracycline-resistant breast cancer.

A trial comparing docetaxel to doxorubicin, one of the most active agents against breast cancer, has also been reported. In this trial, docetaxel 100 mg/m^2 over 1 hour was compared with doxorubicin 75 mg/m^2 in patients with metastatic breast cancer who had failed to respond to an alkylating agent-containing regimen.[115] Docetaxel demonstrated significantly better response rates compared with doxorubicin in this patient population (47 *vs* 32%, p = 0.004). Of the 326 evaluable patients, 49% were classified as having resistant disease, having progressed on prior chemotherapy, 70% of patients received docetaxel or doxorubicin as second-line therapy for metastatic breast cancer, and 30% received this regimen as first-line therapy for metastatic disease after having relapsed >12

Table IV. Randomised trials comparing single agent taxanes with other drugs or combination regimens for metastatic breast cancer

Study	Regimen	Doses (mg/m^2)	OR (%)	TTP	Patient population and comments (n)
Bishop et al.[91]	Pac	200 (3h)	31	5.3 mo	Untreated patients; preliminary report; QOL better with Pac (100)
	CMFP	See legend	19	6.4 mo (p = 0.25)	
Paridaens et al.[110]	Pac	200 (3h)	25	4.2 mo	First-line, anthracycline-naive; crossover study (299)
	Dox	75	41	7.5 mo (p < 0.001)	
Sledge et al.[111]	Pac	175 (24h)	34	5.9 mo	Untreated patients; third arm of study was Pac + Dox (683)
	Dox	60	36	6.2 mo (p = 0.68)	
Dieras et al.[112]	Pac	175 (24h)	17	3.5 mo	Heavily pretreated patients; p = 0.14 (72)
	MMC	12	6	1.6 mo(p = 0.026)	
Nabholtz et al.[113]	Doc	100 (1h)	30	19 wks	Anthracycline-resistant (392)
	MV	See legend	12	11 wks (p = 0.001)	
Chan et al.[115]	Doc	100 (1h)	47	26 wks	Failed alkylating agent regimen; none or 1 prior chemotherapy for metastases (326)
	Dox	75	32	21 wks (p = NS)	
Sjostrom et al.[114]	Doc	100 (1h)	42	6 mo	Anthracycline-resistant; p < 0.001 (199)
	MF	See legend	19	3 mo (p = 0.006)	

CMFP = cyclophosphamide (100 mg/m^2 PO daily days 1 to 14) + methotrexate (40 mg/m^2 IV days 1 and 8) + fluorouracil (600 mg/m^2 IV days 1 and 8) + prednisone (40 mg/m^2 PO daily days 1 to 14); **Doc** = docetaxel; **Dox** = doxorubicin; **h** = duration of infusion in hours; **MF** = methotrexate (200 mg/m^2 IV day 1) + fluorouracil (600 mg/m^2/day days 1 and 8); **MMC** = mitomycin; **mo** = months; **MV** = mitomycin (12 mg/m^2 every 6 weeks) + vinblastine (6 mg/m^2 every 3 weeks); **NS** = not significant; **OR** = overall response; **Pac** = paclitaxel; **QOL** = quality of life; **TTP** = time to progression; **wks** = weeks.

months after adjuvant therapy.[116] These results suggest that docetaxel may be a better agent against breast cancer than doxorubicin. Docetaxel also appears to have activity in patients with breast cancer that exhibits resistance to paclitaxel.[43] However, this effect may be attributable to potency differences between the taxanes, as paclitaxel is rarely given at the maximally tolerated dose. Table IV summarises the trials of single agent taxanes in metastatic breast cancer, and table V outlines comparative information regarding single agent activity of the taxanes in this indication.

5.2 Early Breast Cancer

Many ongoing trials are investigating the role of the taxanes in the treatment of early breast cancer in both the adjuvant and neoadjuvant settings. To date only 1 large randomised trial has matured enough to discuss the data. This trial investigated the impact of dose escalation of doxorubicin or the sequential addition of paclitaxel to an adjuvant regimen in patients with node-positive primary breast cancer.[116] A 3×2 factorial design was utilised to randomise patients between the different doses of doxorubicin (60, 75 or 90 mg/m^2) and the addition of paclitaxel (175 mg/m^2 over 3 hours). In a preplanned interim analysis, no differences in disease-free survival or overall survival were noted with the different doxorubicin doses. However, the addition of paclitaxel reduced the recurrence rate by 22% and the death rate by 26% by multivariate analysis.[116] Kaplan-Meier estimates at 18 months for disease-free survival were 86% (± 1.2%) for the doxorubicin group and 90% (± 1.0%) for the paclitaxel group (unadjusted p = 0.0077).[116] These data will need to be confirmed and patients followed to determine whether this early data will hold up over time. However, based on these results, most clinicians have incorporated paclitaxel into the standard adjuvant regimen for node-positive breast cancer patients. Many other trials are ongoing with similar design and hypothesis. The results of these are anxiously awaited. For patients with node-positive early breast cancer, this is quite an advance and brings hope of improving outcomes for a very large group of patients.

Docetaxel has also entered into clinical trials investigating its use in the adjuvant therapy of breast cancer, both with combination and sequential therapy. These trials are ongoing, but hold promise for the future treatment of breast cancer.

Neoadjuvant therapy with the taxanes has also been prospectively compared with doxorubicin-containing regimens. Paclitaxel for 4 courses has been compared with the combination of fluorouracil, doxorubicin, and cyclophosphamide (FAC) for 4 courses as an induction therapy in patients with operable breast cancer.[117] All patients received 4 courses of FAC postoperatively. Pathological response was evaluated at surgery and was found to be similar between the 2 regimens (none or minimal residual disease in breast, FAC 41% *vs* paclitaxel 32%, p = 0.6; involvement of ≥ 4+ lymph nodes, FAC 20% *vs* paclitaxel 14%, p = 0.46). The dose of paclitaxel in this study was 250 mg/m^2 over 24 hours and was associated with a high rate of febrile neutropenia, requiring prophylactic growth factor or antibacterial support. Ongoing analysis of these patients continues in order to evaluate long term efficacy parameters.

5.3 Taxane Combinations in Breast Cancer

Combinations of the taxanes with many different agents are being used in attempts to overcome resistance to single agents and take advantage of the Goldie-Coldman hypothesis. The most promising of these combinations are the taxanes with doxorubicin. Many trials have now reported the feasibility of these combinations and interesting data have emerged regarding these new regimens. Paclitaxel/doxorubicin combinations have the most data available regarding their clinical activity, but this combination was plagued early in its development with sequencing and scheduling issues. Early trials incorporated prolonged infusions of both drugs, but were associated with pharmacokinetic interactions between the agents that resulted in severe neutropenia and gastrointestinal toxicity (mucositis, typhlitis).[60,118,119] Response rates in these trials were high (80[118] and 72%[119]), but continued use was limited by the toxicity seen with these regimens. Sequence dependence was also demonstrated, with increased gastrointestinal toxicity seen in the groups where paclitaxel preceded doxorubicin, secondary to delayed doxorubicin clearance.[60] Attempts to reduce toxicity and maintain efficacy involved giving both agents as short infusions or bolus, or separating the agents to avoid pharmacokinetic interactions that lead to increased acute toxicity.

Table V. Summary of single-agent activity of taxanes in metastatic breast cancer[79,109]

Patient population	Response rate (%)	
	paclitaxel	docetaxel
First-line therapy	32-62	40-68
1 or more prior therapies for metastatic disease	22-56	36-53
Anthracycline-resistant	21-48	29-57

Gianni et al.[120] were the first to demonstrate a very high response rate of 94% in an early trial utilising bolus administration of doxorubicin 60 mg/m^2 and a short infusion of paclitaxel 200 mg/m^2 over 3 hours. One problem encountered with this combination administered as short infusions is the unacceptably high incidence of congestive heart failure (20%).[120]

The Eastern Cooperative Oncology Group completed a trial comparing single agent doxorubicin (60 mg/m^2 as a 30-minute infusion) with single agent paclitaxel (175 mg/m^2 over 24 hours) or the combination (doxorubicin 50 mg/m^2 as a 30-minute infusion followed 4 hours later by paclitaxel 150 mg/m^2 over 24 hours).[111] The delay between the administration of doxorubicin and paclitaxel appeared to benefit patients in terms of cardiac toxicity: the incidence of grade 3 to 5 cardiac toxicity was no different between the doxorubicin-alone arm and the combination arm (9 *vs* 9%). This trial did not confirm the high response rates seen in earlier trials (doxorubicin 34%, paclitaxel 33%; combination 46%); however, it did demonstrate a superior response rate (p = 0.007 for doxorubicin *vs* combination; p = 0.004 for paclitaxel *vs* combination) and median time to treatment failure for the combination compared with either single agent (median time to treatment failure: doxorubicin 6.2 months; paclitaxel 5.9 months; combination 8.0 months; p = 0.003 for doxorubicin *vs* combination and p = 0.009 for paclitaxel *vs* combination).[111] Overall survival was similar for all 3 arms of the

study (doxorubicin 20.1 months; paclitaxel 22.2 months; combination 22.4 months; p = NS).

Methods to reduce the cardiac toxicity associated with this regimen include substituting epirubicin for doxorubicin, adding dexrazoxane (a cardioprotectant) to the regimen and limiting the cumulative amount of doxorubicin administered. In the bolus combination regimens, if the cumulative dose of doxorubicin is limited to 300 to 360 mg/m^2 and the paclitaxel continued until progression, the response rate is maintained and the incidence of congestive heart failure drops to about 1 to 5%.[120]

Two studies comparing conventional doxorubicin combination regimens with doxorubicin plus paclitaxel have been reported. A French study randomised 247 patients to doxorubicin (60 mg/m^2 intravenous bolus) plus cyclophosphamide (600 mg/m^2 intravenous bolus) [n = 67] or doxorubicin (60 mg/m^2 intravenous bolus) plus paclitaxel (200 mg/m^2 over 3 hours) [n = 180] as neoadjuvant treatment of local-regional breast cancer, with a primary endpoint of pathological complete remissions.[121] Preliminary results from this trial demonstrated an overall response rate of 83% with the doxorubicin + paclitaxel arm versus 66% with doxorubicin + cyclosphosphamide, with 16 and 10% achieving pathological complete response, respectively. At 18 months the disease-free survival was 79% in the doxorubicin + paclitaxel arm and 78% in the doxorubicin + cyclosphosphamide arm of the trial.[122] A second trial comparing doxorubicin + paclitaxel (50 mg/m^2 on day 1 plus 220 mg/m^2 on day 2, respectively) to fluorouracil, doxorubicin, cyclophosphamide (FAC; 500 mg/m^2, 50 mg/m^2, 500 mg/m^2, respectively) as first-line therapy of patients with metastatic breast cancer was recently reported in abstract form. Response rates (68 *vs* 55%, p = 0.032), time to progression (8.3 months *vs* 6.2 months, p = 0.034) and overall survival (22.7 months *vs* 18.3 months, p = 0.02) were significantly higher in the doxorubicin + paclitaxel arms.[123] These results require final analysis and peer review prior to being incorporated into standard practice (see table VI).

Trials are ongoing investigating the role of dexrazoxane in this combination.[125] The optimal dose and schedule of paclitaxel in this combination have yet to be determined in the treatment of breast cancer. Paclitaxel is also being investigated in combination with epirubicin, cyclophosphamide, cisplatin, and fluorouracil ± leucovorin.

Docetaxel with doxorubicin has also been investigated as a potentially active regimen for breast cancer. A single administration schedule is used with this combination and consists of docetaxel administered over 1 hour and either short infusions or bolus injections of doxorubicin. Dieras,[126] in a phase I dose-finding study with docetaxel and doxorubicin, reported response rates of 81% at doses ranging from 40 to 60 mg/m^2 for doxorubicin and 50 to 85 mg/m^2 for docetaxel. The dose-limiting toxicity with the regimen was sepsis and the maximum tolerated dose was docetaxel 75 mg/m^2 over 1 hour and doxorubicin 50 mg/m^2 over 15 minutes, or 60 mg/m^2 of docetaxel and doxorubicin.[126] Interestingly, an excess of cardiac toxicity was not seen with this combination, an advantage over some of the paclitaxel-doxorubicin combinations. This study also limited the cumulative dose of doxorubicin to 300 to 360 mg/m^2 as a part of its schedule. This cumulative dose limit was also incorporated into the Gianni et al.[120] regimen of paclitaxel and doxorubicin, with a similar incidence of cardiac toxicity (1 to 5%).

Ongoing phase III trials comparing this combination to standard regimens for metastatic and primary breast cancer will assist with determining the optimal combination chemotherapy regimen for breast cancer. One such trial is comparing doxorubicin plus docetaxel to the standard regimen doxorubicin plus cyclophosphamide. Preliminary reports regarding this study indicate a superior response (60 *vs* 47%, p = 0.012) and time to progression (37.1 weeks *vs* 31.9 weeks, p = 0.0153) with the docetaxel combination.[124] Overall survival data from this study have yet to be reported. These data require final analysis and confirmation prior to incorporation into standard practice (table VI). Docetaxel is also being investigated in combination with many other chemotherapeutic agents, including epirubicin, vinorelbine, cyclophosphamide,

Table VI. Randomised comparative trials of taxane/doxorubicin and traditional doxorubicin regimens

Study	Regimen	Dose (mg/m^2)	OR (%)	Patient population and comments (n)
Pouillart et al.[121] and Penault-Liorca et al.[122]	Dox + Pac	Dox 60 + Pac 200 (3h)	83	Neoadjuvant therapy for LABC (n = 247); pathological CR = 16% *vs* 10%; 18mo DFS similar (79% *vs* 78%); preliminary results
	Dox + Ctx	Dox 60 + Ctx 600	66	
Pluzanska et al.[123]	Dox + Pac	Dox 50 + Pac 220 (?)	68	Metastatic disease (n = 259); median TTP 8.3 *vs* 6.2mo (p = 0.034); median OS 22.7 *vs* 18.3mo (p = 0.02); abstract data
	FAC	FU 500 + Dox 50 + Ctx 500	55	
Nabholtz et al.[124]	Dox + Doc	Dox 50 + Doc 75 (1h)	60	Metastatic disease (n = 429); median TTP 37.1 *vs* 31.9 wks (p = 0.012); preliminary results
	Dox + Ctx	Dox 60 + Ctx 600	47	

CR = complete response; **Ctx** = cyclophosphamide; **DFS** = disease-free survival; **Doc** = docetaxel; **Dox** = doxorubicin; **FAC** = fluorouracil + doxorubicin + cyclophosphamide; **FU** = fluorouracil; **LABC** = locally advanced breast cancer; **OR** = objective response rate; **OS** = overall survival; **Pac** = paclitaxel; **TTP** = time to progression.

cisplatin, fluorouracil ± leucovorin, and gemcitabine.

Both taxanes are excellent choices for the second-line treatment, and taxane combinations, especially with doxorubicin, for the first-line therapy, of metastatic breast cancer. In patients with anthracycline-resistant breast cancer, docetaxel activity is impressively and consistently high in all trials reported in the literature. Compared with paclitaxel, docetaxel appears to produce superior results in this subset of patients. However, comparisons are indirect and potentially biased because of the lack of direct comparative data.

5.4 Ovarian Cancer

Paclitaxel was first approved for the treatment of metastatic ovarian cancer, and appears to produce response rates of approximately 20 to 37% when given as a single agent.[109] Response rates with combination therapy including paclitaxel have been much higher and have changed the front-line standard of care for advanced ovarian cancer. Although higher doses correlate with higher response rates, the differences in response duration and survival have not been significant.[127] The FDA-approved dose of paclitaxel for ovarian cancer ranges from 135 to 175 mg/m^2. Docetaxel has achieved response rates of 24 to 35% in pretreated ovarian cancer, but is currently not approved for this indication in the US.

5.4.1 First-Line Therapy

Decisions surrounding the choice of first-line systemic therapy for advanced ovarian cancer after optimal surgical debulking are quite difficult. Despite the availability of numerous randomised clinical trials in this setting, many unanswered questions remain. Consensus is found regarding the fact that a combination regimen with a taxane and a platinum compound should be utilised. Controversy lies in the choice of platinum compound, as well as the dose and duration of infusion of paclitaxel.

McGuire et al.[128], in a landmark trial, compared cisplatin plus cyclophosphamide with cisplatin plus paclitaxel in patients with advanced (stage III and IV) ovarian cancer. Eligible stage III patients had more than 1cm of residual disease after initial surgical debulking, a factor associated with poor prognosis. Patients received cyclophosphamide 750 mg/m^2 intravenously with cisplatin 75 mg/m^2 or paclitaxel 135 mg/m^2 intravenously over 24 hours with cisplatin 75 mg/m2 every 3 weeks for a total of 6 courses. Standard premedications were utilised for the paclitaxel arm. The paclitaxel combination was shown to produce superior response rates (73 *vs* 60%) and median survival was prolonged in the paclitaxel arm of the study [38 months (95% CI 32 to 34 months) *vs* 24 months (95% CI 21 to 30); relative risk 0.6 (95% CI 0.5 to 0.8), $p < 0.001$]. Also noted was an increase in toxic events seen with the paclitaxel group, specifically grade 3 to 4 neutropenia (92 *vs* 83%), febrile neutropenia (4 *vs* 0%), alopecia (63 *vs* 37%), and peripheral neurotoxicity (28 *vs* 20%).

These results were confirmed by Piccart et al.[129] in a similar trial of first-line therapy for advanced ovarian cancer. This trial allowed the enrolment of

patients with optimal surgical debulking (<1cm residual disease), did not require second-look laparotomy, used a different dose and infusion schedule of paclitaxel, and the primary endpoint was time to progression. Also, paclitaxel was readily available as salvage therapy when patients relapsed following cisplatin plus cyclophosphamide. Paclitaxel was given over 3 hours at a dose of 175 mg/m^2 with the same dose of cisplatin (75 mg/m^2). In a preliminary analysis, a higher clinical response rate (77 *vs* 66%, p = 0.02) and longer progression-free survival (16 *vs* 12 months, p = 0.0001) were demonstrated with the paclitaxel regimen in patients with both optimal and suboptimal disease.[129] An updated analysis presented at the 1998 Annual Meeting of the American Society of Clinical Oncology demonstrated a significant survival advantage with paclitaxel at a median follow-up of 28 months (median survival 35 *vs* 25 months, p < 0.001).[130] A higher rate of grade 3 neurotoxicity was seen in the paclitaxel arm (18%) compared with the cyclophosphamide arm (1%). Grade 3 to 4 neutropenia was greater in the cyclosphosphamide arm (70 *vs* 56%).

This rate of severe neutropenia was lower than that seen with the paclitaxel arm in the McGuire et al.[128] study and may be secondary to the shorter infusion of paclitaxel utilised in this study (3 *vs* 24 hours). Unfortunately, the incidence of neurotoxicity is limiting with the shorter infusion schedule. Also, the inconvenience of a 24-hour infusion raises issues of patient preference and quality of life associated with these regimens. Continuous infusions are difficult, but not impossible, to administer in the outpatient setting. Many institutions are able to utilise programmable ambulatory pumps for outpatient administration of paclitaxel. However, the issue of cisplatin administration becomes difficult, requiring vigorous hydration that may take many hours to complete. Therefore, many clinicians are searching for alternatives to the paclitaxel/cisplatin regimen that are as effective, but more convenient and better tolerated.

The substitution of carboplatin for cisplatin has been investigated in phase I and II trials, with maximum tolerated doses ranging from 268 mg/m^2 (equivalent to target AUC 5) to 600 mg/m^2 or 696 mg/m^2 (target AUC 10) for carboplatin and 120 mg/m^2 to 250 mg/m^2 for paclitaxel.[131-137] The wide range of maximum tolerated doses may be attributable to differences in dose calculations, treatment schedules, use of colony-stimulating factors and patient characteristics. The major toxicities associated with this regimen appear to be myelosuppression and neurotoxicity. Clinical response rates range from 70 to 100%. However, these phase I and II data may overestimate the efficacy of this combination and should be interpreted with caution. Direct comparisons of carboplatin plus paclitaxel to cisplatin plus paclitaxel are currently underway. Interim analyses are available for 2 such studies, the Dutch/Danish trial[138] and the German-Austrian trial.[139]

The Dutch/Danish trial administered paclitaxel (175 mg/m^2 over 3 hours) followed by cisplatin (75 mg/m^2) or paclitaxel in the same dose and schedule followed by carboplatin (target AUC 5). In the preliminary analysis of 148 patients, no significant differences were found in efficacy, but grade 3 to 4 neutropenia and thrombocytopenia was more common in the carboplatin arm (44 *vs* 82% and 10 *vs* 16%, respectively). The incidence of grade 3 to 4 neurotoxicity was similar between the 2 groups (4 *vs* 4%). The German-Austrian trial compared carboplatin (target AUC 6) plus paclitaxel (185 mg/m^2 over 3 hours) to cisplatin (75 mg/m^2) plus paclitaxel (185 mg/m^2 over 3 hours). In a preliminary analysis of 488 evaluable patients, no significant differences were seen between the 2 groups in terms of clinical response rates and progression-free survival. The carboplatin arm was associated with an increased incidence of myelosuppression, including grade 3 to 4 neutropenia and thrombocytopenia (13 *vs* 5% and 3 *vs* <1%, respectively). The cisplatin arm demonstrated a higher incidence of nonhaematological toxicity, including grade 3 to 4 myalgias/arthralgias (6 *vs* 3%), nausea/vomiting (16 *vs* 5%), ototoxicity (2 *vs* 0%), and peripheral neuropathy (8 *vs* 6%). Quality of life was determined using the EORTC QLQ 30 tool. Results from this analysis showed that patients on the cisplatin arm had significantly inferior quality of life during

treatment compared with the carboplatin arm (p = 0.008).

Firm conclusions from these 2 trials cannot be made until the final analyses are published. However, the authors state that the combination of carboplatin and paclitaxel appears to be feasible and more convenient compared with cisplatin/paclitaxel. The use of similar combinations is currently being investigated in early stage ovarian cancer. Currently, adjuvant systemic chemotherapy for stage I and II ovarian cancer patients is not recommended.

Sequential administration of these agents has also been investigated with interesting results. A Gynecologic Oncology Group trial comparing single agent cisplatin 100 mg/m^2 or paclitaxel (200 mg/m^2 over 24 hours) to the combination (cisplatin 75 mg/m^2 plus paclitaxel 135 mg/m^2 over 24 hours) in untreated patients with suboptimal stage III/IV ovarian cancer demonstrated an inferior response of paclitaxel alone (RR 46%) compared with cisplatin alone (RR 74%) or the combination (RR 72%).[140] The median progression-free survival was also significantly longer with cisplatin or the combination compared with paclitaxel. Overall survival did not differ between groups. Allowance of crossover treatment on the single-agent arms may account for similar survival between the 3 groups in spite of differences in progression-free survival. The importance of a platinum compound in the regimen is emphasised by these data, and this currently remains the standard of care for advanced ovarian cancer. Although these data demonstrated the inferiority of single agent paclitaxel compared with combination therapy (cisplatin/paclitaxel), the issue of single agent cisplatin versus combination therapy has yet to be resolved. The authors state that the number of patients able to complete all 6 cycles was greater in the combination arm and fewer delays and dose changes were required in this arm. However, this difference did not appear to positively influence progression-free survival. The issue of sequential versus combination therapy is a controversy for many different tumour types. Further investigation may lead to better understanding of these effects. Until that time, combination therapy with a taxane and a platinum compound appears to be more acceptable in this setting.

Substituting docetaxel for paclitaxel in these regimens may allow for less neurotoxicity. Two phase II studies incorporating docetaxel into a platinum-containing regimen have been reported in abstract form.[141,142] Guastalla et al.[141] evaluated the efficacy of the combination of docetaxel and cisplatin (75 mg/m^2 of each agent) in 45 patients with chemotherapy-naive ovarian cancer with stage III/IV disease. Response was evaluated in 44 patients by second look laparotomy, finding 50% of patients with a pathological complete response or microscopic residual lesions. Median disease-free survival was 16 months. The main toxicity was neutropenia, with 80% of patients experiencing grade 3 to 4 neutropenia. The incidence of neurotoxicity was low in this trial (any grade, 26%; grade 2, 4%) and 40 out of 44 evaluable patients (91%) received 6 cycles.

In another phase II trial, investigators combined docetaxel with cisplatin and cyclophosphamide.[142] This 3-drug regimen was given to 31 patients with chemotherapy-naive, stage III/IV ovarian cancer (mean number of cycles 6). The overall response rate with this combination was high (81%; complete response 50%, partial response 31%) and the regimen was relatively well tolerated. The main toxicity was again neutropenia, with 100% of patients experiencing grade 3 to 4 neutropenia. Grade 2 neurosensory toxicity was seen in 29% of patients and grade 2 to 3 asthenia was seen in 65% of patients.[142]

These 2 studies are preliminary reports of important trials, which require further investigation and comparison with paclitaxel combinations. The lower incidence of neurotoxicity may not be clinically significant in light of the increased neutropenia and asthenia seen with the docetaxel combinations. Results from other trials investigating these and other docetaxel combinations in the treatment of advanced ovarian cancer are eagerly awaited.

5.4.2 Refractory or Relapsed Disease

Prognosis for patients who relapse after primary systemic therapy is poor. Many different salvage regimens are utilised in this setting. Decisions re-

garding which therapy is the best are controversial and dependent on prior exposure to chemotherapy, particularly a platinum compound. In a randomised trial comparing paclitaxel to combination therapy with cyclophosphamide, doxorubicin, and cisplatin in patients with advanced ovarian cancer more than 12 months after an initial response to platinum, overall response rates were higher with the platinum-containing regimen (54 *vs* 49%).[143] This trial indicated the importance of a platinum compound, even in patients who have recurrent disease after a similar regimen. The role of the taxanes in this setting is not clear at this time. In a recent study comparing paclitaxel (175 mg/m^2 over 3 hours) with topotecan (1.5 mg/m^2/day × 5 days), ten Bokkel Huinink et al.[144] demonstrated a significantly longer time to progression with topotecan (23 *vs* 14 weeks, p = 0.002) despite similar response rates (topotecan 20.5 *vs* paclitaxel 13.2%, p = 0.138) and duration of response (topotecan 32 *vs* paclitaxel 20 weeks, p = 0.222).

Docetaxel also appears to have considerable activity against ovarian cancer. Two studies reported partial and complete responses in previously treated patients with platinum-resistant tumours, with a range of 24 to 35%.[99,100] This appears to be significant in patients with cisplatin-resistant tumours. Other investigators have described case series of patients with ovarian cancer responding to docetaxel after prior platinum exposure.[101]

Table VII summarises studies with the taxanes in advanced ovarian cancer.

5.4.3 Intraperitoneal Therapy

Paclitaxel has been administered into the peritoneum in patients with residual disease following standard chemotherapy. An ongoing Gynecologic Oncology Group trial investigating the question of clinical activity with this type of therapy has completed accrual and awaits final analysis. The role for this type of administration is controversial, but remains an option for individual patients who meet specific criteria. Intraperitoneal administration of docetaxel has not been reported to date. Combination therapy with cisplatin and other agents is also being studied with docetaxel in the treatment of ovarian cancer with hopes of improving the standard of care.

Table VII. Comparative activity of taxanes for advanced ovarian cancer

Study	Regimen	Doses (mg/m^2)	OR (%)	Patient population and comments (n)
Guastalla et al.[141]	Doc + CDDP	75 + 75	50	Phase II trial; responses were pathological CR or minimal residual disease; chemotherapy-naive stage III/IV patients; median DFS = 16mo (44)
Jakobsen et al.[142]	Doc + CDDP + Ctx	75 + 75 + 500	81	Phase II trial; chemotherapy-naive stage III/IV patients; CR 50% (31)
Colombo et al.[143]	Pac	175 (3h)	49	Relapse >12 months after response to platinum (79)
	CAP	See legend	54	
ten Bokkel Huinink et al.[144]	Pac	175 (3h)	13	Longer TTP (23 *vs* 14 wks) with topotecan (226)
	Topotecan	1.5/day × 5	21	
Muggia et al.[140]	Pac	200 (24h)	46	Suboptimal stage III-IV; Pac significantly less OR (615)
	CDDP	100	74	
	Pac + CDDP	135 (24h) + 75	72	
McGuire et al.[128]	Pac + CDDP	135 (24h) + 75	73	First-line chemotherapy; suboptimal FIGO Stage III or IV; significantly longer median PFS and OS; results confirmed[97] (216)
	CDDP + Ctx	75 + 750	60	
Neijt et al.[138]	Pac + CDDP	175 (3h) + 75	NA	Reference states that 'no differences were found in efficacy' but no response data given (190)
	Pac + Carbo	175 (3h) + AUC 5		

AUC = area under the concentration-time curve (used as target for carboplatin dose); **CAP** = cyclophosphamide 500 mg/m^2 + doxorubicin 50 mg/m^2 + cisplatin 50 mg/m^2; **Carbo** = carboplatin; **CDDP** = cisplatin; **CR** = complete response; **Ctx** = cyclophosphamide; **DFS** = disease-free survival; **Doc** = docetaxel; **FIGO** = Federation Internationale de Gynecologie et d'Obstetrique; **NA** = not available; **OR** = overall response; **OS** = overall survival; **Pac** = paclitaxel; **PFS** = progression-free survival; **TTP** = time to progression.

6. Conclusions

In developing a risk-benefit model for decision making, the task of comparing agents is always difficult if there are no direct comparative trials to lead the analysis. This is the case with the taxanes, as with many other classes of anticancer medications. In light of this apparent lack of information, clinicians are forced to make comparisons with the available data.

Both agents appear to have similar toxicity and risks associated with their use, similar to those with most chemotherapeutic agents. Indirect evidence and intertrial comparisons appear to indicate a slight advantage of docetaxel over paclitaxel in terms of efficacy (response rates). However, combination regimens incorporating either agent do not appear to result in any significant difference in antitumour response. An ongoing trial directly comparing the taxanes in metastatic breast cancer is underway, but because of dose considerations (docetaxel 100 mg/m^2 over 1 hour versus paclitaxel 175 mg/m^2 over 3 hours) will not adequately answer the question of which agent is superior. Another ongoing trial is investigating the differences between administration every week and every 3 weeks for both agents in a 4-arm study design for adjuvant therapy of early breast cancer. Preclinical and clinical data indicate a lack of complete cross-resistance between these agents, with differing but partially overlapping toxicity. Administration of docetaxel after a patient's tumour has progressed on paclitaxel has demonstrated a significant response rate of 18%.[43] However, the dose utilised with docetaxel is usually the maximum tolerated dose (100 mg/m^2) and differences in response rates and lack of cross-resistance may only represent potency differences between the 2 agents.

Both agents have similar activity in the setting of advanced ovarian cancer, but the majority of data are with paclitaxel alone or in combination. Currently, the recommendation for first-line therapy of advanced ovarian cancer is the combination of paclitaxel and a platinum compound. Most of the controversy lies in the choice of the platinum compound (cisplatin versus carboplatin) and the dose and administration schedule of paclitaxel. Because of improved tolerability, many experts utilise carboplatin and paclitaxel as the standard regimen. Docetaxel has also been utilised in place of paclitaxel in similar combination regimens. Preliminary data regarding docetaxel are promising, but require further investigation to better delineate the role of docetaxel in advanced ovarian cancer.

Many ongoing clinical trials are attempting to answer questions that may assist in the decision making process. Pharmacoeconomic evaluation of these agents has been attempted.[145-147] However, direct comparisons are lacking between the taxanes and indirect comparisons are fraught with bias and uncertainty. Until data from ongoing comparative trials are available, pharmacoeconomic analyses do little to assist in treatment decisions, but are interesting tools to have in the event that better comparative data become available. At this time, these agents appear to be complimentary to each other rather than competitive in the arena of breast and ovarian cancer.

It is difficult to recommend one agent over the other, but it is evident that these agents differ in many ways. Familiarity with these nuances allow the clinician the opportunity to make an educated decision regarding treatment for breast or ovarian cancer.

The taxanes are a wonderful example of our attempt to incorporate new found knowledge into the standards of today. It took several decades to unravel the intricacies of these agents and today we still have many unanswered questions surrounding their mechanisms of action and resistance, pharmacokinetics, optimal dose and administration, clinical efficacy and place in therapy. Although these are important aspects of care to investigate, the amount of information available regarding other commonly prescribed chemotherapeutic agents pales in comparison to the wealth of information available with the taxanes, and the rate at which these data have become available is astonishing. With the incorporation of the taxanes into mainstream oncology, the standard of care has been improved in patients with both breast and ovarian cancers, as well

as many other neoplasms. When ongoing clinical trials addressing the unknown issues are completed, more information will be available to use these agents better and again improve outcomes for our patients. Today, understanding and utilising the data available are key to managing patients with cancer and optimising the use of healthcare resources.

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