

THE DEVELOPMENT AND CLINICAL UTILITY OF THE TAXANE CLASS OF ANTIMICROTUBULE CHEMOTHERAPY AGENTS

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ABSTRACT

The taxane class of antimicrotubule anticancer agents is perhaps the most important addition to the chemotherapeutic armamentarium against cancer over the past several decades. After only a brief period, the taxanes have not only demonstrated a unique ability to palliate the symptoms of many types of advanced cancers, including carcinoma of the ovary, lung, head and neck, bladder, and esophagus, they have also demonstrated effectiveness in the initial therapy of earlier stages of cancer, a setting in which any new therapy is likely to make its greatest impact. The challenge now facing investigators is to develop strategies to maximize therapeutic benefits with the taxanes in the early stages, as well as the advanced stages, of many cancers. This review describes the preclinical features and clinical results of the two major taxanes, paclitaxel (Taxol®, Bristol-Myers Squibb) and docetaxel (Taxotere®, Rhone-Poulenc Rhorer).

HISTORY AND CHEMISTRY

The prototypic taxane, paclitaxel, was discovered as part of a National Cancer Institute program in which extracts of thousands of plants were screened for

anticancer activity (1). Paclitaxel was initially supplied from the bark of the scarce Pacific yew, *Taxus brevifolia*, which had deleterious long-term environmental implications. However, alternate sources, particularly an approved semisynthetic process using a readily available precursor, 10-deacetylbaaccatin III, derived from the needles of more abundant yew species such as the European yew *Taxus baccata*, is currently meeting commercial demands. Docetaxel is derived semisynthetically from 10-deacetylbaaccatin III and is slightly more water soluble than paclitaxel is (2). Both paclitaxel and docetaxel consist of a complex taxane ring linked to an ester at the C-13 position (Figure 1). The moieties at the C-2' and C-3' positions on the C-13 side chain are essential for their antimicrotubule activity.

MECHANISMS OF ACTION AND RESISTANCE

The binding site for the taxanes on microtubules is distinct from those of GTP, colchicine, podophyllotoxin, and vinblastine. Paclitaxel binds to the N-terminal 31 amino acids of the beta-tubulin subunit of tubulin polymers (3). Unlike the vinca alkaloids, which prevent microtubule assembly, the taxanes decrease the lag time and shift the dynamic equilibrium between tubulin dimers and microtubules toward polymerization, thereby stabilizing microtubules (4). These effects occur even in the absence of GTP- and microtubule-associated proteins, which are usually essential for this function. Docetaxel has a 1.9-fold higher affinity for the site than paclitaxel does and it induces tubulin polymerization at a 2.1-fold lower critical tubulin concentration (5). The initial slope of the assembly reaction and the amount of polymer formed is also greater for docetaxel. In addition, docetaxel is more potent than paclitaxel is at inducing cytotoxicity in vitro and in tumor xenografts (6). These differences do not imply that docetaxel has a greater therapeutic index because greater potency may also portend greater toxicity, and pharmacologic differences between the agents must be considered.

The taxanes inhibit cell proliferation by inducing a sustained mitotic block at the metaphase/anaphase boundary, as well as formation of an incomplete metaphase plate of chromosomes and an abnormal organization of spindle microtubules, which occur at much lower drug concentrations than those required to increase microtubule mass (7). Aberrant mitotic spindles and mitotic block due to stabilization of microtubule dynamics results from inhibitory drug effects on intrinsic microtubule processes involving the equilibrium between tubular dimers and microtubule polymers such as dynamic instability and treadmilling. After the disruption of microtubules, particularly those comprising the mitotic spindle apparatus, the precise means by which cell death occurs are not clear. However, morphologic features and DNA fragmentation patterns characteristic of programmed cell death or apoptosis have been documented in

tumor cells after taxane treatment (7). These apoptotic effects have been associated with phosphorylation of *bcl-2*, an antiapoptotic protein, resulting in a disruption of the balance between the dimerization of *bcl* and *bax* proteins (8).

Both paclitaxel and docetaxel have also been shown to enhance the cytotoxic effects of ionizing radiation *in vitro* at clinically achievable concentrations, which may be due to the inhibition of cell-cycle progression in the G₂ and M phases, the most radiosensitive phases of the cell cycle (9).

Two mechanisms of acquired resistance to the taxanes *in vitro* have been described. First, some tumors contain alpha- and beta-tubulin, which have an impaired capacity to polymerize into microtubules and an inherently slow rate

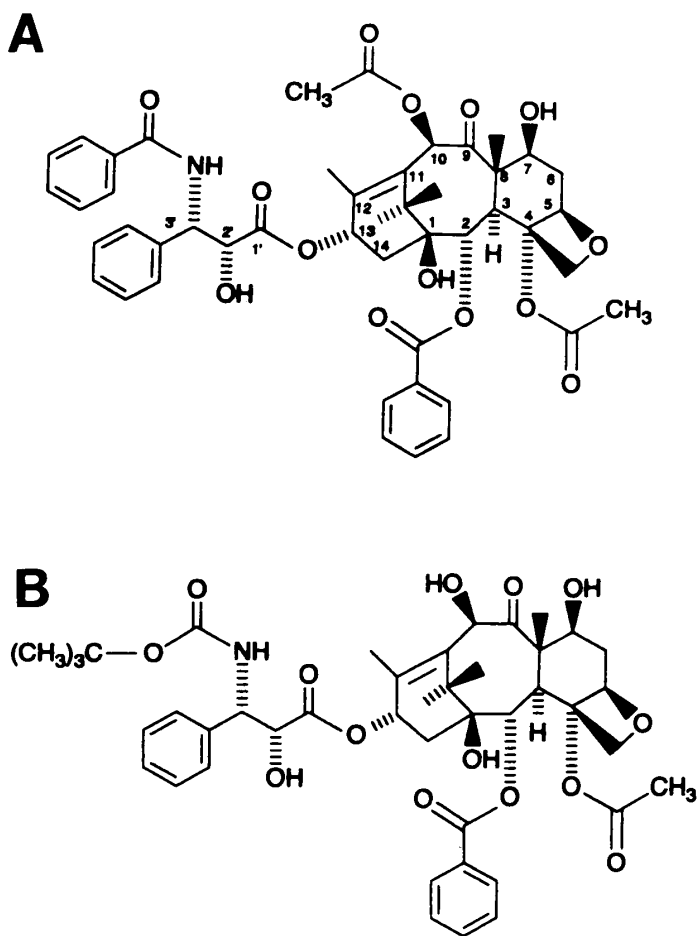


Figure 1 Structures of the taxanes: (A) paclitaxel and (B) docetaxel.

of microtubule assembly in the absence of the taxanes (10). A second mechanism, multi-drug resistance (MDR) that involves amplification of membrane phosphoglycoproteins that function as drug efflux pumps, confers varying degrees of cross-resistance to diverse, structurally bulky natural product cytotoxins (11). MDR can be reversed by many types of agents, including the main components of the formulation vehicles of both paclitaxel and docetaxel, Cremophor EL (polyoxyethylated castor oil) and Tween 80 (polysorbate 80), respectively (12, 13). The clinical relevance of these mechanisms of resistance is not known, but the early results of studies in breast cancer suggest a lack of complete cross-resistance between the taxanes and anthracyclines that would not be expected if MDR is an important mechanism of resistance for this particular tumor (14). Taxane resistance has also been related to differential expression of various tubulin isotypes, decreased microtubule bundle formation, decreased expression of *bcl-2*, and other mechanisms that are unrelated to MDR (8, 15–17).

CLINICAL RESULTS

Pharmacology

Paclitaxel and docetaxel share the following pharmacologic characteristics: large volumes of distribution, rapid uptake by most tissues, long half-lives of elimination, and substantial hepatic disposition. The pertinent pharmacokinetic parameters of both agents are summarized in Table 1.

PACLITAXEL The pharmacokinetic behavior of paclitaxel appeared linear in early studies of prolonged schedules, but clearance has been shown to be nonlinear or saturable, particularly on shorter schedules, with both plasma concentrations and drug exposure increasing disproportionately with increasing doses (18). Plasma levels that are achieved are capable of inducing relevant effects *in vitro*. Despite extensive plasma protein binding, paclitaxel is readily cleared from plasma. The volume of distribution is large, most likely due to avid drug binding to tubulin, which is ubiquitous. Renal clearance is insignificant, whereas hepatic P-450 mixed function oxidative metabolism, biliary excretion, fecal elimination, and tissue binding are responsible for the bulk of systemic clearance (18). In animals, paclitaxel is distributed to all tissues except classical tumor sanctuary sites such as testes and the central nervous system.

As part of the effort to combine paclitaxel with cisplatin after prominent single agent activity was noted in advanced ovarian cancer, the possibility of sequence-dependent drug interactions was studied (19). Neutropenia was shown to be most severe when cisplatin was administered before paclitaxel, which may be due to a reduction in paclitaxel's clearance, possibly caused by

the modulating effects of cisplatin on cytochrome P-450 enzymes. Since the least toxic sequence, paclitaxel followed by cisplatin, was also more cytotoxic to tumor cells in vitro (20), it was specifically selected for subsequent clinical studies (21). Sequence-dependent effects have been described with the paclitaxel-doxorubicin (more toxicity and reduced doxorubicin clearance when paclitaxel precedes doxorubicin) and paclitaxel-cyclophosphamide regimens (more toxicity when paclitaxel precedes cyclophosphamide) (22, 23). These effects have been noted only with prolonged (24 h) schedules of paclitaxel. Sequence-dependent cytotoxic effects have also been observed in vitro between paclitaxel and melphalan, etoposide, 5-fluoruracil, estramustine, and gallium nitrate.

Other intriguing drug interactions have also been observed. For example, the combination of paclitaxel and carboplatin seems to produce equivalent neutropenia and less thrombocytopenia than either carboplatin or paclitaxel alone (24). Less toxicity and greater efficacy have also been noted in animal tumor models following treatment with the combination of vinorelbine and either paclitaxel or docetaxel compared with any of these agents alone (25, 26).

Table 1 Summary of the pharmacologic characteristics of paclitaxel and docetaxel^a

Characteristic	Paclitaxel	Docetaxel
Pharmacokinetic behavior	Nonlinear	Linear
Optimal linear model	2–3 compartments	2–3 compartments
Elimination half-life		
2 compartments	~7 h	~12 h
3 compartments	~20 h	~13 h
Volume of distribution at steady state	Large, ~182 liters/m ²	Large, ~74 liters/m ²
Peak plasma concentrations	~5 μ M (175 mg/m ² over 3 h) ~10 μ M (250 mg/m ² over 3 h) ~0.5 μ M (175 mg/m ² over 24 h)	~3 μ M (100 mg/m ² over 1 h)
Plasma protein binding	>95%	>90%
Tissue distribution	Extensive except CNS and testes	Extensive except CNS
Systemic clearance	~350 ml/min/m ²	~300 ml/min/m ²
Renal clearance	Minor, <5–10%	Minor, <5–10%
Hepatic clearance	Significant, 70–80% in feces	Significant, 70–80% in feces
Nature of hepatic disposition	Inactivation, hydroxylation, cytochrome P450, primarily CYP3A	Inactivation, oxidation, cytochrome P450, primarily CYP3A
Drug interactions	P450 inducers and inhibitors	P450 inducers and inhibitors

^aFrom References 18, 27, and 48. CNS, Central nervous system.

DOCETAXEL The pharmacokinetic behavior of docetaxel at relevant dose-schedules ($<115 \text{ mg/m}^2$ over 1 h) is linear, and plasma disposition is triexponential (27, 28). Like paclitaxel, docetaxel avidly binds to plasma proteins ($>90\%$), peak plasma concentrations exceed levels that induce relevant effects *in vitro*, and tissue distribution is extensive (27). Fecal excretion accounts for 70%–80% of total drug disposition in animals, whereas renal excretion accounts for $<10\%$. Docetaxel is metabolized by hepatic cytochrome P-450 mixed function enzymes (29). Except for the combination of docetaxel and cisplatin, which is not associated with sequence dependence, sequence-dependent effects between docetaxel and other cytotoxic agents have not been thoroughly evaluated, though the potential for interactions with drugs that affect cytochrome P-450 enzymes, as well as other chemotherapy agents, has been demonstrated *in vitro* (29).

Administration, Dose, and Schedule

PACLITAXEL The most important issues regarding the use of paclitaxel are optimal dosing and scheduling. The duration of treatment, particularly the duration of drug exposure above a relevant threshold concentration, appears to be the most important factor influencing cytotoxicity *in vitro* (18, 24). The clinical development of paclitaxel was initially limited to the 24-h schedule due to the high rate of major hypersensitivity reactions (HSR) in studies using short schedules without premedication (1, 21). Therefore, most available data regarding antitumor activity pertain to the 24-h schedule, which was the first schedule to be approved. However, prominent antitumor activity has also been noted with shorter schedules, particularly the 3-h schedule. Although both schedules have been shown to be equivalent in the setting of recurrent ovarian cancer (30), inferences cannot be made about their equivalence in other tumor types and settings at this time. Impressive activity has also been noted with more prolonged schedules (i.e. 96-h schedule in advanced breast cancer) (31), and even shorter schedules [i.e. 1-h schedule in advanced non-small cell lung cancer (NSCLC) (32)].

Paclitaxel is generally administered at a dose of 175 mg/m^2 over 3 h or $135\text{--}175 \text{ mg/m}^2$ over 24 h every three weeks to treat patients with advanced cancers of the ovary and breast. Most early phase II studies utilized higher doses, 250 mg/m^2 over 24 h, which usually caused severe neutropenia and often required hematopoietic growth factors (1). It should be emphasized that adequate studies of dose-response have not been completed in many tumors. The following doses have been recommended on less orthodox schedules: 200 mg/m^2 over 1 h as either a single dose or as three daily divided doses every three weeks, and 140 mg/m^2 over 96 h every three weeks (31, 32). The following premedication is recommended to prevent major HSR: dexametha-

sone, 20 mg orally or intravenously (i.v.) 12 and 6 h before treatment; diphenhydramine, 50 mg i.v. 30 min before treatment; and an histamine H₂-antagonist such as cimetidine (300 mg), famotidine (20 mg), or ranitidine (150 mg) i.v. 30 min before treatment.

The importance of hepatic metabolism and biliary excretion in paclitaxel disposition suggests that doses should be modified in patients with hepatic dysfunction. Although official dose modifications have not been formulated, preliminary studies indicate that moderate elevations in serum concentrations of hepatocellular enzymes and/or bilirubin increase the likelihood of developing severe toxicity, and it seems prudent to reduce paclitaxel doses by at least 50% in patients with moderate or severe hyperbilirubinemia and/or elevations in hepatocellular enzymes (18). As expected based on the minimal contribution of renal clearance to overall clearance, dose modifications do not appear to be required in patients with severe renal insufficiency (18).

DOCETAXEL Although several administration schedules were studied during phase I development, docetaxel has been exclusively evaluated at a dose of 100 mg/m² as a 1-h i.v. infusion every three weeks (27, 33). Lower doses (60–75 mg/m²) may produce less toxicity; however, the relative therapeutic advantage of high versus low doses is not clear. Despite the use of a polysorbate 80 formulation instead of Cremophor EL, which is the putative constituent of paclitaxel's formulation vehicle and is responsible for major HSR, high rates of HSR and fluid retention following docetaxel infusion led to the use of several premedication regimens, the most popular of which is dexamethasone, 8 mg orally twice daily for five days starting one day before docetaxel with or without both H₁- and H₂-histamine antagonists given i.v. 30 min before docetaxel (27, 33).

Docetaxel clearance was found to be reduced by approximately 25% in patients with elevations in serum concentrations of both hepatocellular enzymes (>1.5-fold) and alkaline phosphatase (>2.5-fold), regardless of whether or not the elevations were due to hepatic metastases, and more toxicity was noted. Dose reductions by at least 25% are recommended for such patients, though more substantial reductions may be required in the case of hyperbilirubinemia (33, 34).

Toxicity

PACLITAXEL Many obstacles were encountered during early trials that threatened the prospects for paclitaxel's further development, particularly major HSR. Neutropenia was the principal toxicity, but several other toxicities and unique pharmaceutical properties were encountered (35).

Hypersensitivity reactions A difficult problem encountered during early drug development was the high incidence of major HSR, manifested by dyspnea with bronchospasm, urticaria, and hypotension (1, 35, 36). Serious reactions usually occurred within 2–3 min after drug administration, and almost all HSR occurred within the first 10 min after treatment with the first or second dose. Most patients recovered fully after discontinuation of paclitaxel and occasionally after treatment with antihistamines, fluids, and vasopressors. Although as many as 40% of patients developed flushing and rashes, minor HSR do not portend the development of major reactions.

HSR were initially felt to be mediated by the direct release of histamine or other vasoactive substances, analogous to the HSR caused by radiographic contrast agents (35, 36). Although HSR could have been caused by paclitaxel itself or its Cremophor EL vehicle, the latter was felt to be responsible since it induces histamine release and similar HSR in dogs. Other drugs formulated in Cremophor EL are associated with similar reactions (35, 36). Early trials were completed using 24-h infusions and premedication with corticosteroids and histamine H₁- and H₂-antagonists since similar regimens have been effective in preventing repeated reactions to radiographic contrast agents. With standard premedication, the incidence of major HSR has decreased to less than 3% (30, 35). A study of the relative safety and efficacy of two different paclitaxel doses (135 vs 175 mg/m²) and two schedules (24 vs 3 h) with standard premedication has shown that the overall incidence of major HSR was low and similar (2.1 vs 1.0%) in the 3- and 24-h groups, respectively, indicating that premedication is the most important prophylactic measure (30).

Hematological toxicity Neutropenia is the main toxicity of paclitaxel (1, 35). The onset of neutropenia is usually day 8–10 and recovery is typically complete by day 15–21. Neutropenia is not cumulative, suggesting that paclitaxel does not irreversibly affect immature hematopoietic cells. At doses of 200–250 mg/m² given over 24 h, neutropenia is usually severe even in patients who have not received prior myelosuppressive therapy. However, fever and infections are uncommon. This dose range was initially recommended for phase II studies because the duration of severe neutropenia (<500/μl) was usually short (<5 days) and treatment delays for unresolved toxicity were rare. Although fevers and infectious sequelae were originally reported to be low (<10% of courses) at these doses, these complications occurred more frequently in later studies (1, 35). Therefore, granulocyte colony-stimulating factor (G-CSF) is often given to prevent complications of neutropenia in trials of doses in the 200–250 mg/m² range. In most patients, particularly those who had received large doses of other chemotherapy agents previously, the maximum tolerated dose without G-CSF is 175 to 200 mg/m². The most critical pharmacological determinant of the

severity of neutropenia is the duration that plasma concentrations are maintained above a critical threshold level, which may explain why neutropenia is more severe with longer schedules (37, 38). This does not imply that shorter infusions should always be used since the optimal dose and schedule have not been determined for most tumors. Paclitaxel alone rarely causes severe thrombocytopenia and anemia.

Neurotoxicity Paclitaxel induces a peripheral neuropathy that is typified by a glove-and-stocking distribution of sensory symptoms such as numbness and paresthesia and symmetric distal loss of sensation carried by both large (proprioception, vibration) and small (pin prick, temperature) fibers (35, 39, 40). Symptoms may begin as soon as 24–72 h after treatment with higher doses (>250 mg/m²), but they usually occur only after multiple courses at conventional doses. Neurotoxicity may be more severe with shorter schedules (41). Although severe neurotoxicity precludes increasing paclitaxel doses above 250 mg/m², severe effects are rare at conventional doses, even in patients who previously received other neurotoxic agents such as cisplatin (42). Motor and autonomic dysfunction may also occur, especially at high doses and in patients with preexisting neuropathies caused by diabetes mellitus and alcoholism. In addition, optic nerve effects such as scintillation scotomata may occur (43). Transient myalgia, usually noted 2–5 days after therapy, is also common, and a myopathy may occur with high doses of paclitaxel combined with cisplatin (39, 40).

Cardiac effects Although cardiac rhythm disturbances have been observed, the importance of these effects is not known (35, 44, 45). The most common effect is bradycardia, which is rarely associated with hemodynamic compromise and does not appear to be an indication for discontinuing therapy. Mobitz types I (Wenckebach syndrome) and II and third-degree heart block have also been noted, but the incidence in a large database was only 0.1% (45). All events were asymptomatic, reversible, and noted in trials that required continuous cardiac monitoring, suggesting that cardiac effects are underreported. It is likely that bradyarrhythmias are caused by paclitaxel, since related taxanes affect cardiac automaticity and conduction, and similar disturbances have occurred in humans and animals after the ingestion of yew plants (45).

Myocardial ischemia, atrial arrhythmias, and ventricular tachycardia have also been noted (35, 44, 45). Whether there is a direct causal relationship between paclitaxel and these effects is uncertain (45). There is also no clear evidence that paclitaxel induces cumulative toxicity nor that it augments the cardiac effects of the anthracyclines. Preliminary data also indicate that it does not worsen myocardial function in patients with marginal ventricular function (46). However, the frequency of congestive cardiotoxicity in patients treated

with paclitaxel (3-h schedule) and doxorubicin may be higher than expected compared to the anthracyclines alone (22). Therefore, potential drug effects on ventricular function should be evaluated at lower cumulative anthracycline doses than might otherwise be done with anthracyclines alone in patients treated with both agents, and patients treated with the combination of doxorubicin and paclitaxel, particularly 3-h schedules, should not receive cumulative doses of doxorubicin above 360 mg/m^2 until additional data are available. Although the precise risks for cardiotoxicity are not known, routine cardiac monitoring during treatment does not seem to be necessary, but it is advisable for patients who may not be able to tolerate bradyarrhythmias.

Miscellaneous toxicities Nausea, vomiting, and diarrhea are infrequent (1, 21, 35). Higher doses may cause mucositis, especially in patients with leukemia who may be more prone to mucosal barrier disruption and in patients with prolonged (96 h) infusions (31, 47). Paclitaxel also induces reversible alopecia of the scalp, and loss of all body hair occurs with cumulative therapy. Inflammation at the injection site and along the course of an injected vein and in areas of drug extravasation and skin reactions over previously radiated sites occur rarely.

DOCETAXEL *Myelosuppression* A reversible, noncumulative neutropenia is the principal toxicity of docetaxel. At a dose of 100 mg/m^2 , neutrophil counts are usually below $500/\mu\text{l}$. The incidence of severe neutropenia and sequalae appear to be much less with lower docetaxel doses, but only limited data are available (27, 33). The severity of neutropenia does not seem to be related to schedule, but there has been only limited experience with infusion durations greater than 1 h. Significant effects on platelets and erythrocytes are uncommon.

Hypersensitivity Although docetaxel is not formulated in Cremophor EL, HSR have been reported in as many as 33% of patients receiving docetaxel without premedication (27, 33, 48). Like paclitaxel, major HSR typically occur during the first two courses and within minutes after treatment and generally resolve within 15 min after cessation of treatment. Most HSR, though, are minor. Both the incidence and severity of HSR appear to be reduced by following premedication with corticosteroids and H₁- and H₂-histamine antagonists.

Fluid retention A unique fluid retention syndrome, characterized by edema and third-space fluid collections (e.g. pleural effusions, ascites), may occur with docetaxel. It is most likely due to increased capillary permeability (27, 33, 48). In early studies in which prophylactic medication was not used, fluid retention was rarely significant at cumulative docetaxel doses $<400 \text{ mg/m}^2$, but the incidence of severe toxicity increased sharply at cumulative doses $>400 \text{ mg/m}^2$,

often resulting in treatment delay or termination. However, prophylactic treatment with corticosteroids with or without H₁- and H₂-histamine antagonists appears to significantly reduce the incidence of severe effects and increase the number of courses before the onset of this toxicity (see above) (48). Fluid retention generally resolves slowly after docetaxel is stopped. Early recognition and treatment with potent diuretics is increasingly being used successfully to manage fluid retention. The incidence of fluid retention may be reduced by using lower single doses (60–75 mg/m²). Overall, these measures have resulted in a substantial increase in the ability to use docetaxel as part of general practice.

Miscellaneous Skin toxicity may occur in 50–75% of patients (27, 33, 48). However, premedication may reduce the overall incidence. A erythematous pruritic maculopapular rash that affects the forearms and hands is typical. Other cutaneous effects include desquamation of the hands and feet, palmar-plantar erythrodyesthesia that may respond to pyridoxine or cooling, and onchodystrophy characterized by brown discoloration, ridging, oncholysis, soreness, and brittleness of the fingernails. Alopecia occurs in most patients.

Docetaxel produces peripheral neurotoxicity similar to that produced by paclitaxel. Although mild to moderate manifestations are frequent, severe toxicity is uncommon following repetitive treatment with docetaxel doses <100 mg/m², except in patients with antecedent disorders such as alcohol abuse. Myalgias are often noted in the peritreatment period, and malaise is a common complaint. There is no convincing evidence that directly links docetaxel to cardiac disturbances, but the potential for subclinical cardiac effects has not been evaluated as thoroughly as with paclitaxel. Stomatitis, albeit uncommon, is more frequent with docetaxel than with paclitaxel. Vomiting and diarrhea may also be observed, but severe toxicity is rare.

Anticancer Activity

Although paclitaxel is further along in its clinical development, both paclitaxel and docetaxel seem to have similar spectra of clinical activity. Both agents have consistently shown impressive activity in advanced cancers of the ovary, breast, lung, esophagus, bladder, and head and neck. Early reports of activity in other cancers require confirmation. The challenge that is now facing investigators is to develop strategies using the taxanes as first-line therapy in cancers where cure or improved survival may be achievable.

OVARIAN CANCER Paclitaxel was initially approved for the treatment of epithelial ovarian cancer based on the results of single-agent trials of the 24-h schedule. These trials provided the impetus for studies in other tumor types. In the first five studies, 20–48% of women with refractory or recurrent disease responded [defined as either a complete response (CR), meaning complete

disappearance of all evidence of disease, or a partial responses (PR), meaning reduction in all disease by at least 50%] (42, 49–52). Overall, 32% of women who were considered resistant to platinum analogs (disease progression during or within six months) and 38% of those who relapsed more than six months after treatment with regimens containing platinum analogs responded to paclitaxel (21). These results were much better than those of other salvage therapies and were comparable to the early results of studies with platinum analogs, which have been the mainstay of therapy. The generalizability of these results to the treatment of this disease in general oncology practice was demonstrated in a National Cancer Institute program in which paclitaxel (24-h schedule) was initially provided for women whose cancers had progressed after treatment with three regimens. Of the first 1000 patients, 22% responded despite their poor prognostic characteristics (53).

With the demonstration that paclitaxel and cisplatin could be safely combined (19), a regimen consisting of paclitaxel (24-h schedule) followed by cisplatin was compared with a standard regimen of cyclophosphamide and cisplatin in untreated women with stage IV or III ovarian cancer (54). Clinical responses occurred in 60 and 73% of women in the cyclophosphamide and paclitaxel groups, respectively ($P = 0.01$), and paclitaxel was associated with a modest improvement in surgically defined CR, 26 vs 20% ($P = 0.08$). The paclitaxel regimen reduced the risk of recurrence by 32%, and the median duration of progression-free survival was 18 and 13 months in the paclitaxel and cyclophosphamide groups, respectively. More importantly, survival was significantly longer ($P < 0.001$) in the paclitaxel group (median, 38 vs 24 months), suggesting that it should become the new standard therapy for the initial treatment of advanced ovarian cancer. Current studies address the relative benefits of carboplatin versus cisplatin and whether the efficacy of the paclitaxel-cisplatin regimen could be improved by using shorter (3 h) or more prolonged (96 h) paclitaxel schedules. Untreated patients are also being randomized to treatment with either paclitaxel and cisplatin, cisplatin alone, or paclitaxel alone to determine whether the drugs are more effective in combination or individually.

Two important issues—whether the schedule of administration of paclitaxel (short versus long infusions) is important from either a toxicologic or a therapeutic standpoint and whether a dose-response relationship exists in the usual dosing range—are also being studied in refractory and recurrent ovarian cancer. In a phase III study that was previously discussed in which patients were randomized to treatment with two different paclitaxel doses (135 vs 175 mg/m²) and two different schedules (24 vs 3 h) given with premedication (see above), progression-free survival was significantly longer in the high-dose group than in the low-dose group [19 vs 14 weeks ($P = 0.02$)], but survival was

similar in both dose and schedule groups (30). Although regulatory approval was originally granted for paclitaxel doses of 135 mg/m^2 on a 24-h schedule for refractory and recurrent ovarian cancer, these results were the impetus for the subsequent approval of paclitaxel doses of 175 mg/m^2 on a 3-h schedule. Preliminary results of another trial in which women with platinum-resistant cancer were randomized to treatment with paclitaxel doses of either 135 or 250 mg/m^2 (plus G-CSF) over 24 h (55) indicated a slightly higher response rate in the high-dose arm compared to the low-dose arm (36 vs 28%); however, there was no survival advantage. A meta-analysis of phase II trials has also not demonstrated a positive relationship between paclitaxel dose and response (56).

Docetaxel has not been studied as extensively as paclitaxel in advanced ovarian carcinoma, particularly in combination with other agents or as first-line therapy. However, four phase II studies of docetaxel doses of 100 mg/m^2 given every three weeks involving 206 patients demonstrated response rates ranging from 25–41% (27, 33, 57–60). Like paclitaxel, docetaxel is active in disease that is refractory to platinum compounds. Among 51 patients with platinum-refractory disease in one study, a 41% response rate was noted (57), and subgroup analysis of platinum-refractory patients in another trial demonstrated a response rate of 35%, with a median duration of five months (60).

BREAST CANCER The prominent antitumor activity of the taxanes in metastatic breast cancer was initially demonstrated for paclitaxel (24-h schedule) (61, 62). In the first study, 56% of women who had received no more than one prior chemotherapy regimen for metastatic disease responded to paclitaxel doses of 200–250 mg/m^2 , and the median progression-free interval was nine months (61). A response rate of 62% was noted in a second trial in which paclitaxel doses of 250 mg/m^2 and G-CSF were given to women who had previously received either adjuvant therapy only or no prior therapy, confirming the high level of activity (62). Impressive response rates of 32–38% have also been reported with a 3-h schedule of paclitaxel (175–250 mg/m^2) (63, 64). In addition, docetaxel (75–100 mg/m^2) has shown significant activity as first-line therapy in metastatic disease, with response rates of 52–68% (65–68). The likelihood of responding has not been related to hormonal receptor status or to whether patients had received prior adjuvant therapy. Responses in visceral metastatic sites, especially liver, have also been high with both taxanes.

The encouraging results with the taxanes are comparable to those reported in early studies of the anthracyclines, which are among the most active agents in breast cancer. However, gauging the overall importance of these results and the ultimate role of the taxanes in breast cancer, a relatively responsive tumor was difficult initially since early studies were performed in women who had

received little prior therapy, unlike the situation in ovarian cancer. Nevertheless, the prominent activity of both taxanes in heavily pretreated patients has confirmed the initial high level of enthusiasm, though the likelihood of responding is indirectly related to the extent of prior therapy (14, 69, 70). At one center, response rates following treatment with moderate doses of paclitaxel (24-h schedule) ranged from 38% in women who received one prior regimen to 17% in women who received at least three prior regimens (14, 69, 70). As second-line therapy, docetaxel doses of 100 mg/m² have also produced striking activity, with response rates ranging from 50–58% (71–73). Perhaps the most impressive results with the taxanes have been in women whose disease progressed during prior therapy with the anthracyclines. Among 68 such patients treated with docetaxel (100 mg/m²) in two trials, the response rate was 51% (71, 72). Although responsiveness in this situation seems to be greater with docetaxel, the doses of paclitaxel and docetaxel used in this setting may not be comparable since docetaxel has been evaluated at doses that generally induce more profound toxicity. However, similar activity (response rate, 44%) has been observed with a lower docetaxel dose (60 mg/m²) (74). Still, the impressive activity with both taxanes in this refractory setting implies that they may make an even greater impact in early disease settings.

Further studies of the taxanes in breast cancer will focus on defining their roles in earlier stages and, ultimately, in adjuvant therapy after local treatment of early stage disease. To accomplish this objective, the Eastern Cooperative Oncology Group has recently completed enrollment in a study in which untreated women with metastatic disease were randomized to treatment with either paclitaxel or doxorubicin alone or both agents combined. If the combination is determined to be superior, it will be incorporated into trials evaluating the role of paclitaxel in adjuvant therapy. In another study of the role of paclitaxel in adjuvant therapy, high-risk patients are being treated with either high, moderate, or low doses of cyclophosphamide and doxorubicin followed by either paclitaxel or no further treatment. The feasibility of combining the taxanes with other active agents such as doxorubicin, cyclophosphamide, cisplatin, vinorelbine, and 5-fluorouracil is also being evaluated (14). Combinations of the taxanes and anthracyclines appear especially promising (22, 75). In a phase I trial of paclitaxel (3-h schedule) and doxorubicin, 94% of untreated patients with metastatic breast cancer responded and 41% had CR; however, the high incidence of cardiac effects requires further study (see above) (22).

Optimal dosing is also being studied in metastatic breast cancer. The early results of a randomized trial of paclitaxel at 135 or 175 mg/m² (3-h schedule) indicated no differences in response rates [29 (high dose) vs 22% (low dose)] or in median survival [11.7 (high dose) vs 10.5 months (low dose)], although progression-free survival was longer with the higher dose [4.2 vs 3 months (*P*

= 0.02)] (76). These results led to the regulatory approval of paclitaxel doses of 175 mg/m² (3-h schedule) in metastatic disease after failure of combination chemotherapy or relapse within six months of adjuvant therapy. In another study evaluating whether higher doses portend greater activity, women with metastatic breast cancer are being randomized to treatment with paclitaxel doses of either 175, 210, or 250 mg/m² (3-h schedule). Although there has been a paucity of studies addressing optimal dosing with docetaxel, this issue is important because docetaxel has almost exclusively been evaluated at a dose of 100 mg/m², which induces severe neutropenia in most patients, and substantial activity with less toxicity has been noted at lower doses (60–75 mg/m²).

Optimal scheduling has been studied in a randomized trial in which women with metastatic breast cancer were treated with either 3- or 24-h infusions of paclitaxel (175 mg/m²) (41). There were no differences in response rates (29 vs 31%), median progression-free survival (3.5 vs 4.6 months), or survival (9.8 vs 13.4 months) between the 3- and 24-h groups, respectively. However, the starting doses were escalated in more women treated with 3-h infusions due to minimal toxicity at the starting dose. It is also important to note that response rates in patients receiving paclitaxel over 3- and 24-h schedules were more disparate in women who had no prior therapy (34 vs 57%) compared with those who had adjuvant therapy only (36 vs 40%) or therapy in both adjuvant and metastatic settings (24 vs 22%). In another study, women with metastatic breast cancer are being treated with either 3- or 24-h schedules of paclitaxel (250 mg/m²) with G-CSF, which are more equitoxic dose schedules than those in the prior study. Perhaps the most illustrative support for the importance of schedule are reports of responses to treatment with prolonged (96 h) schedules of paclitaxel in women with metastatic breast cancer whose disease progressed on shorter taxane schedules. Similar studies of alternate docetaxel schedules have not been performed.

LUNG CANCER Both paclitaxel and docetaxel have demonstrated favorable results in untreated patients with stage IIIB and IV NSCLC. In one of the original studies, a 24% response rate, a median response duration of 28 weeks, and a median survival of 40 weeks (56 weeks for responders) were noted following treatment with high paclitaxel doses ranging from 200 to 250 mg/m² (24-h schedule) (77). In another randomized trial, response rates were 21, 0, and 2% for paclitaxel and the investigational agents merbarone and piroxantrone, respectively (78). The median duration of response to paclitaxel was 6.5 months, the 1-year survival rate was 41.7%, and the median survival was 24.1 weeks. Activity has also been noted with shorter schedules, including response rates of 26 and 23% in untreated and previously treated patients, respectively, who were treated with paclitaxel on a 1-h schedule (32).

Docetaxel has also demonstrated impressive activity in NSCLC. In a review of phase II trials (33), docetaxel doses of 100 mg/m^2 produced cumulative response rates of 31 and 19% in patients who were chemotherapy-naive and previously treated, respectively (79–83). Lower doses of docetaxel ($60\text{--}75 \text{ mg/m}^2$) have resulted in responses in 19–25% of untreated patients (84, 85).

The taxanes have also shown striking activity in small cell lung cancer. Paclitaxel doses of 250 mg/m^2 (24-h schedule) without and with G-CSF has produced responses in 34 and 41% of chemotherapy-naive patients with extensive disease, respectively (86, 87). Similar activity has also been noted with docetaxel in small cell lung cancer. In one study, responses occurred in 25% of patients, the majority of whom had prior chemotherapy and/or radiotherapy (88).

Because of the favorable activity of both taxanes as single agents in advanced lung cancer, the development of taxane-based combination regimens is an area of major interest. Perhaps the most exciting regimen is that of the combination of the taxanes and platinum compounds. In view of the safety and activity of cisplatin combined with either paclitaxel and docetaxel in pilot studies (89–92), the efficacy of such regimens is being evaluated. A phase III trial in untreated patients with stage IV NSCLC that compared standard therapy consisting of etoposide plus cisplatin with cisplatin plus 24-h infusions of paclitaxel given at either a low dose or a high dose plus G-CSF revealed significantly ($P < 0.001$) higher response rates for both paclitaxel arms compared with standard therapy (32 vs 27 vs 12%) and no significant difference in median survival times (9.6 vs 10 months) between the paclitaxel-based regimens, though median survival was longer than these compared with the standard arm (7.7 months) (93). The study also incorporated quality of life assessments to determine whether the increased toxicity and resources expended with higher drug doses and G-CSF are warranted. Another promising regimen is the combination of paclitaxel and carboplatin. In a phase II trial in untreated advanced NSCLC, paclitaxel (24-h schedule) plus carboplatin resulted in a response rate of 62%, a CR rate of 9%, and impressive survival rates (median progression-free survival time, 28 weeks; median survival, 53 weeks; 1-year survival rate, 54%) (94). Although the feasibility and activity with taxane-based regimens may portend improved palliation of advanced disease, incorporation of novel regimens into the multimodality therapy of early disease may lead to even greater effects on survival. Since paclitaxel has been shown to enhance the effects of ionizing radiation *in vitro*, locally advanced lung cancer may also be an ideal setting to evaluate the feasibility and benefits achieved by combining these modalities (95).

HEAD AND NECK CANCER Both paclitaxel and docetaxel have demonstrated impressive activity in patients with locally recurrent or metastatic squamous cell

carcinoma of the head and neck. In one phase II trial, 43% of chemotherapy-naïve patients responded to paclitaxel (250 mg/m^2) with G-CSF, which compares favorably with response rates achieved with standard agents (96). A response rate of 26% has also been reported in patients with nasopharyngeal carcinoma (97). Additionally, response rates ranging from 32–42% in advanced head and neck cancer have been reported with docetaxel (100 mg/m^2) (98, 99). Further development of the taxanes in head and neck cancer will include assessments of high versus low doses of the taxanes alone and in combination regimens and evaluations of various schedules of the taxanes in combination with other active drugs such as the platinum compounds and 5-fluorouracil.

OTHER CANCERS Although the taxanes were active in melanoma in preclinical studies and activity was noted in phase I trials, marginal response rates of 12–18% and 13–17% occurred with paclitaxel and docetaxel, respectively, in phase II studies (1, 21, 100, 101). Paclitaxel was inactive in colorectal, renal, prostate, pancreatic, gastric, and brain cancers (1, 21, 102). Although docetaxel showed no activity in colorectal and renal cancers, response rates ranging from 20–29% and 14–24% have been noted in pancreatic and gastric cancers, respectively (27, 33, 103–106). Interesting, some taxane-based combination regimens have resulted in impressive activity in cancers that have not been responsive to the taxanes alone, such as paclitaxel and estramustine in advanced prostate cancer (107). Both paclitaxel and docetaxel appear to be modestly active in locally recurrent or metastatic squamous cell carcinoma of the cervix, with response rates of 17 and 14%, respectively (108, 109). A modest response rate of 17% has been reported with paclitaxel in non-Hodgkin's lymphoma in one study, whereas 14 and 29% of primary refractory and relapsed non-Hodgkin's lymphomas, respectively, responded in another trial (110, 111).

Beneficial effects have also been noted with paclitaxel (24-h schedule) and G-CSF in patients with germ cell, bladder, and esophageal cancers. In one study, 42% of patients with advanced transitional cell carcinoma of the bladder responded (112). A 32% response rate was also noted in patients with advanced esophageal carcinoma, despite a low level of activity with paclitaxel in other gastrointestinal cancers (113). In addition, a 24% response rate has been observed in patients with cisplatin-resistant germ cell malignancies (114). Although phase II results with docetaxel in these tumor types are less mature, docetaxel doses of 100 mg/m^2 have demonstrated an impressive response rate of 50% in previously untreated patients with advanced transitional cell carcinoma of the bladder (115). The agent has also demonstrated modest activity (response rate, 18%) as second-line therapy in patients with advanced soft tissue sarcoma (116), whereas impressive activity with response rates as high as 53% has been reported with paclitaxel in patients with advanced Kaposi's sarcoma (117).

FUTURE DIRECTIONS

The antitumor spectrum of the taxanes appears to be the broadest of any class of anticancer agents. The demonstration of prominent activity in patients with advanced stages of many refractory cancers implies that the taxanes may play an even greater role in early stage disease, which is the setting in which any novel agent has the potential of making its greatest impact on survival and cure. The significant prolongation in survival that has been demonstrated for paclitaxel as part of first-line treatment in patients with advanced ovarian cancer is such an example. Similar impacts in more common malignancies such as breast and ovary may translate into substantial advantages in cancer therapy. In addition, the recognition of the novel mechanism of action and the utility of the taxanes has increased our appreciation of the potential of antimicrotubule agents in the treatment of cancer.

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