REVIEW ARTICLE

DRUG THERAPY

ALASTAIR J.J. WOOD, M.D., *Editor*

PACLITAXEL (TAXOL)

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THE taxanes are an important new class of anticancer agents that exert their cytotoxic effects through a unique mechanism. Paclitaxel (Taxol), the first taxane in clinical trials, is active against a broad range of cancers that are generally considered to be refractory to conventional chemotherapy. This has led to the regulatory approval of paclitaxel in the United States and many other countries for use in the palliative therapy of patients with ovarian and breast cancers resistant to chemotherapy. The challenge now is to develop strategies using paclitaxel in the initial therapy of cancers in which cure or improved survival may be an achievable goal.

Paclitaxel was discovered as part of a National Cancer Institute program in which extracts of thousands of plants were screened for anticancer activity. In 1963, a crude extract from the bark of the Pacific yew *Taxus brevifolia,* a scarce and slow-growing evergreen found in the old-growth forests of the Pacific Northwest, was found in preclinical studies to have cytotoxic activity against many tumors.[1] Paclitaxel was identified as the active constituent of this extract in 1971.[1] Although it had a novel chemical structure (Fig. 1) and broad preclinical activity, development was slowed because it did not appear to be more effective against experimental tumors than other agents under development at that time. In addition, it was expected that the procurement and preparation of this potentially scarce natural product in sufficient quantities for large-scale development would be arduous. Interest was revived in 1979 when paclitaxel's unique mechanism of action as an antitumor drug was identified, and was further stimulated when impressive activity was demonstrated in the National Cancer Institute tumor screening.[2-4]

MECHANISMS OF ACTION AND RESISTANCE

Microtubules are composed of polymers of tubulin in dynamic equilibrium with tubulin heterodimers composed of alpha and beta protein subunits.[4-6] Although their principal function is the formation of the mitotic spindle during cell division, microtubules are also involved in many vital interphase functions, including the maintenance of shape, motility, signal transmission, and intracellular transport.[4-7] Unlike other antimicrotubule drugs, such as vinca alkaloids, which induce the disassembly of microtubules, paclitaxel promotes the polymerization of tubulin.[2,3,8-14] At subnanomolar concentrations, paclitaxel inhibits the disassembly of microtubules, whereas it increases their mass and numbers at higher, albeit clinically achievable, concentrations.[14] The microtubules formed in the presence of paclitaxel are extraordinarily stable and dysfunctional, thereby causing the death of the cell by disrupting the normal microtubule dynamics required for cell division and vital interphase processes. Paclitaxel also induces the expression of the gene for tumor necrosis factor α, but structure–activity studies indicate that these activities are not related to paclitaxel's effects on microtubule assembly, raising the issue of what part these cytokines play in the antitumor activity of paclitaxel.[15] The binding site for paclitaxel is distinct from the binding sites for guanosine triphosphate, colchicine, vinblastine, and podofilox (podophyllotoxin).[4,8-11,15] Paclitaxel binds to the N-terminal 31 amino acids of the beta-tubulin subunit in the microtubule, rather than to tubulin dimers.[8,9,16,17] In intact cells, paclitaxel induces the bundling of microtubules, which may be a useful clinical correlate of a lethal drug effect,[3,4,18-20] and the formation of large numbers of asters of mitotic spindles (Fig. 2).[4,18-21] It also enhances the cytotoxic effects of ionizing radiation in vitro, possibly by inducing arrest in the premitotic G_2 and mitotic phases of the cell cycle, which are the most radiosensitive phases.[22,23] The feasibility of using paclitaxel in combination with radiation to treat patients with locally advanced lung, head and neck, and esophageal cancers, which are responsive to both kinds of treatment, is currently being evaluated.[24]

Two mechanisms of acquired resistance to the taxanes have been characterized. First, some tumors contain alpha- and beta-tubulin with an impaired ability to polymerize into microtubules and have an inherently slow rate of microtubule assembly that is normalized by the taxanes.[25] A second mechanism involves the amplification of membrane phosphoglycoproteins that function as drug-efflux pumps.[26,27] The multidrug-resistant phenotype of tumor cells confers varying degrees of cross-resistance to various structurally bulky natural products, including anthracyclines, etoposide, vinca alkaloids, colchicine, and taxanes. The contribution of these mechanisms to clinical drug resistance is not known, but the results of early clinical studies of patients with breast cancer suggest a lack of complete

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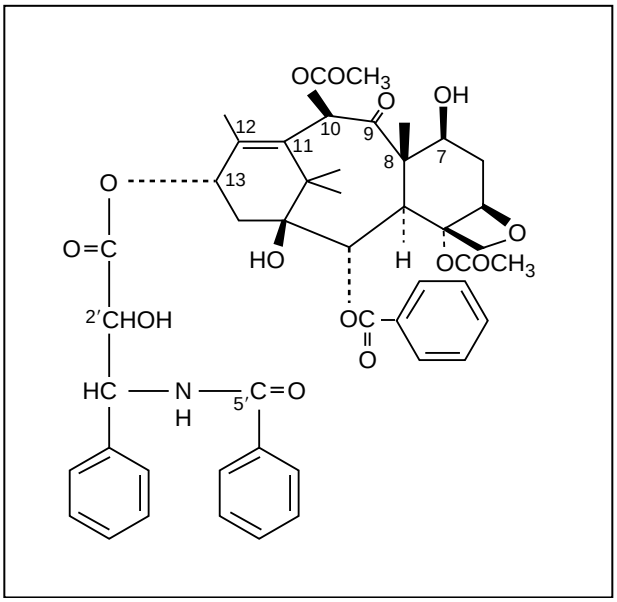

Figure 1. Structure of Paclitaxel.

cross-resistance between the taxanes and anthracyclines that would not be expected if the multidrug-resistant phenotype was an important mechanism of resistance.

Toxicity

In the early phase 1 trials, a number of obstacles, particularly hypersensitivity reactions, were encountered that threatened the prospects for paclitaxel's further development. Table 1 shows the results of phase 1 trials of paclitaxel as a single agent that have been performed in the United States.[28-40] Neutropenia was the principal toxic effect, but several others were encountered, along with unique pharmaceutical properties.[4,41,42]

Hypersensitivity Reactions

A difficult problem encountered during the early development of paclitaxel was the high incidence of major hypersensitivity reactions, approaching 25 to 30 percent in some studies. Most affected patients had type 1 hypersensitivity reactions, including dyspnea with bronchospasm, urticaria, and hypotension.[43] Serious reactions usually occurred within 2 to 3 minutes after the administration of paclitaxel, and almost all occurred within the first 10 minutes. The majority occurred after the first or second dose. One fatality was reported; all other patients recovered fully after the discontinuation of paclitaxel and with occasional treatments with antihistamines, fluids, and vasopressors. Although flushing and rashes have also been noted in as much as 40 percent of patients, minor reactions do not portend the development of major ones.[44,45]

Initial observations suggested that these hypersensitivity reactions were mediated by the direct release of histamine or other vasoactive substances, as are the hypersensitivity reactions caused by radiographic contrast agents.[4,41,43] Although these reactions could have been caused by paclitaxel itself or its polyoxyethylated castor oil vehicle (Cremophor EL), the latter was thought to be responsible, since it induced histamine release and similar manifestations in dogs[46] and since other drugs formulated in polyoxyethylated castor oil, such as cyclosporine and vitamin K, have been associated with similar reactions.[44,47] The phase 1 trials were completed with the use of 24-hour infusions and premedication with corticosteroids and histamine H_1 and H_2 antagonists, since similar regimens have proved effective in preventing repeated reactions to radiographic contrast agents. This schedule has been used in the majority of phase 2 and 3 studies, as well. The following premedication is currently recommended: 20 mg of dexamethasone orally or intravenously 12 and 6 hours before treatment; 50 mg of diphenhydramine intravenously 30 minutes before treatment; and a histamine H_2 antagonist such as cimetidine (300 mg), famotidine (20 mg), or ranitidine (150 mg) intravenously 30 minutes before treatment. Although these measures are not fully protective, the incidence of major hypersensitivity reactions has decreased to approximately 1 to 3 percent.[41,44] The National Cancer Institute of Canada Clinical Trials Group evaluated the relative safety and efficacy of two paclitaxel doses (135 and 175 mg per square meter of body-surface area) and two infusion schedules (for 24 hours and for 3 hours) with standard premedication in women with recurrent or refractory ovarian cancer.[45] The overall incidence of major hypersensitivity reactions was similar in women receiving paclitaxel for 3 hours (2.1 percent) and in those receiving it for 24 hours (1.0 percent), with premedication. These findings will have a substantial impact if the antitumor activity of the 3-hour and 24-hour infusions is equivalent, as initially reported in these patients, since shorter infusions are more convenient and less expensive. Patients with major hypersensitivity reactions who have been rechallenged with paclitaxel after receiving high doses of corticosteroids have not had recurrences, although this approach has not been universally successful.[48,49]

Hematologic Toxicity

Neutropenia is the principal toxic effect of paclitaxel.[41] Its onset is usually on day 8 to 10 after treatment, and recovery is usually complete by day 15 to 21. Neutropenia is not cumulative, suggesting that paclitaxel does not irreversibly damage immature hematopoietic cells. At doses of 200 to 250 mg of paclitaxel per square meter given over a period of 24 hours, neutropenia is usually severe even in previously untreated patients, with neutrophil counts decreasing to below 500 per cubic millimeter after the majority of infusions. This dose range was initially recommended for phase 2 studies because the duration of severe neutropenia (<500 per cubic millimeter) was usually short (<5

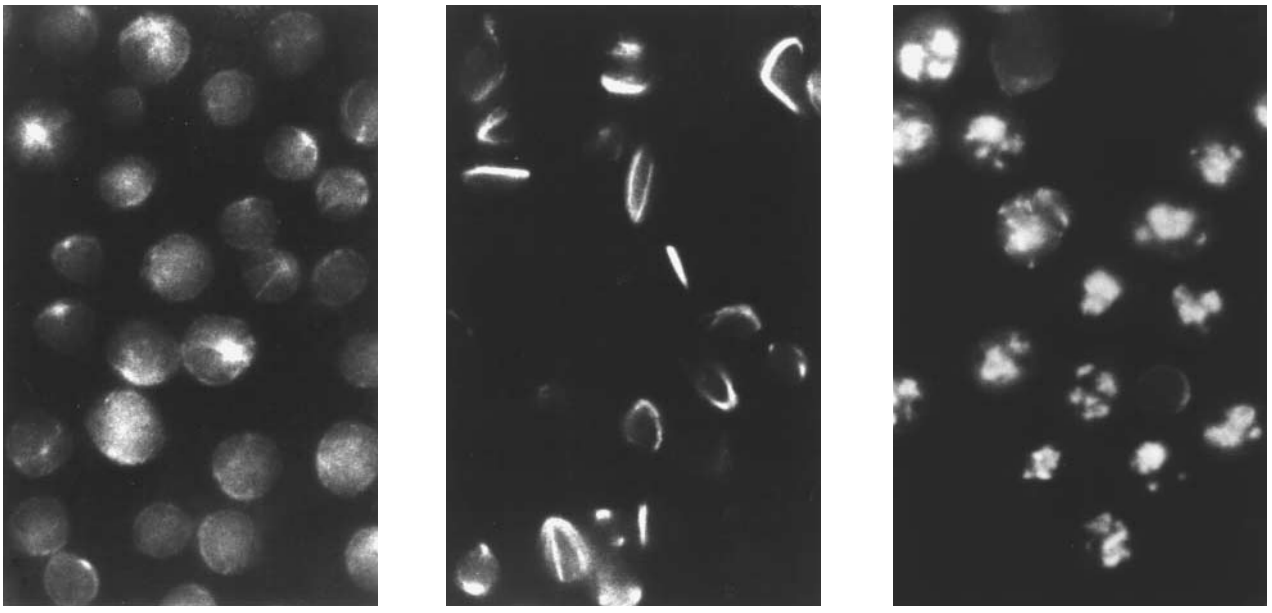

Figure 2. Microtubule Effects of Paclitaxel in Human Leukemia Cells Stained with Antitubulin Antibody and Viewed by Indirect Immunofluorescence Microscopy (×3780).

Panel A shows untreated K562 cells; Panel B, microtubule bundles in HL-60 promyelocytic leukemia cells treated with paclitaxel; and Panel C, multiple asters of mitotic spindles in K562 cells treated with paclitaxel.[18]

days) and treatment delays for unresolved toxic effects were rare. Although the frequency of febrile and infectious sequelae at these doses was originally reported to be lower (<10 percent of courses) than that of severe neutropenia,[50,51] these complications occurred more frequently in later studies. Therefore, granulocyte colony-stimulating factor is commonly given to prevent the complications of neutropenia in trials of doses in this range. In most patients, particularly those who have received large doses of other chemotherapeutic agents previously, the maximal tolerated dose without granulocyte colony-stimulating factor is 175 to 200 mg per square meter. The most critical pharmacologic determinant of the severity of neutropenia seems to be the length of time that plasma drug concentrations are higher than biologically active concentrations (0.05 to 0.1 μmol per liter) — a fact that may explain why neutropenia is more severe with longer infusions.[45,52] This does not imply that shorter infusions should be used in all patients, since the optimal dose and schedule have not been determined for most tumors. Notwithstanding these differences, the principal clinical determinant of the severity of neutropenia is the extent of previous myelotoxic therapy. Paclitaxel alone rarely causes severe thrombocytopenia and anemia.

Neurotoxicity

Paclitaxel induces a peripheral neuropathy that is characterized by sensory symptoms such as numbness and paresthesia in a glove-and-stocking distribution.[41,53] There is often symmetric distal loss of sensation carried by both large fibers (proprioception, vibration) and small ones (temperature, pinprick). Symptoms may begin as soon as 24 to 72 hours after treatment with higher doses (>250 mg per square meter) but usually occur only after multiple courses at conventional doses (135 to 250 mg per square meter). Severe neurotoxicity precludes the administration of paclitaxel doses above 250 mg per square meter over a period of 3 or 24 hours, but severe neurotoxicity is rare at conventional doses (<200 mg per square meter), even in patients who have previously received other neurotoxic agents, such as cisplatin. For example, although mild-to-moderate neurotoxicity was reported in 0 to 88 percent of women with recurrent ovarian cancer after receiving paclitaxel in doses of up to 175 mg per square meter, severe toxic effects occurred in only 0 to 3 percent despite prior therapy with cisplatin in the majority.[50,54,55] The distal, symmetric, length-dependent neurologic deficits suggest that paclitaxel causes a sensory and motor axonal loss similar to the "dying-back" neuropathies that may have their origin in the cell body or in axonal transport, but a few patients have the simultaneous onset of symptoms in the arms and legs, involvement of the face (perioral numbness), the predominance of large-fiber loss, and diffuse areflexia suggestive of a neuronopathy. Both types of neuropathy depend on the dose of paclitaxel or its combination with cisplatin.[53,56] 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 disturbances, characterized by scintillating scotomata,

Table 1. Phase 1 Studies of Paclitaxel in the United States.*

Study	Duration of Infusion (Premedication)†	Recommended Phase 2 Dose	Dose-Limiting Toxic Effect	Other Toxic Effects
Legha et al.[28]	1 hr ×5 days (no)	40 mg/m² ×5	Neutropenia	Alopecia, diarrhea
Grem et al.[29]	1–6 hr ×5 days (no)	30 mg/m² ×5	Neutropenia	Hypersensitivity reactions, nausea, vomiting, mucositis, thrombocytopenia
Kris et al.[30]	3 hr (no)	190 mg/m²‡	Hypersensitivity reactions	Neutropenia, nausea
Schiller et al.[31]	3 hr (yes)	210 mg/m²	Neutropenia	Neurotoxicity
Schiller et al.[31]	3 hr + G-CSF (yes)	250 mg/m² + 5 μg of G-CSF/kg/day	Neurotoxicity	—
Donehower et al.[32]	1–6 hr (yes)§	210 mg/m²	Neutropenia	Neuropathy, mucositis, myalgia, hypersensitivity reactions
Brown et al.[33]	6 hr (no)	225 mg/m²	Neutropenia	Myalgia, neuropathy, mucositis, hypersensitivity reactions
Wiernik et al.[34]	1–6 hr (yes)§	250 mg/m²	Neutropenia	Mucositis, neuropathy, hypersensitivity reactions
Wiernik et al.[35]	24 hr (yes)	250 mg/m²	Neutropenia	Hypersensitivity reactions, neuropathy
Ohnuma et al.[36]	24 hr (no)	200 mg/m²¶	Neutropenia	Nausea, vomiting
Hurwitz et al.[37]	24 hr (yes)¶	350 mg/m²	Neurotoxicity	Neutropenia, mucositis, thrombocytopenia
Rowinsky et al.[20]	24 hr (yes)‖	310 mg/m²	Mucositis	Neutropenia, neuropathy, hypersensitivity reactions
Sarosy et al.[38]	24 hr + G-CSF (yes)**	250 mg/m² + 10 μg of G-CSF/kg/day	Neuropathy	Neutropenia, cardiac toxicity, thrombocytopenia, myalgia
Wilson et al.[39]	96 hr (no)††	140 mg/m²	Mucositis, neutropenia	—
Spriggs and Tondini[40]	120 hr (no)	150 mg/m²	Neutropenia	Mucositis

*G-CSF denotes granulocyte colony-stimulating factor, the doses of which are indicated per kilogram of body weight.

†Courses were repeated every 21 days except in the study by Rowinsky et al.,[20] in which courses were repeated every 14 to 21 days. Treatment was continued until the disease progressed, serious toxic reactions occurred, or the patient withdrew from the study.

‡This was the highest dose given in studies that were terminated because of major hypersensitivity reactions.

§The duration of the infusion was lengthened during the study, and premedication was added because of major hypersensitivity reactions.

¶The patients were children with refractory solid tumors.

‖The patients had refractory leukemia.

**The patients had advanced-stage ovarian cancer that was recurrent or refractory to treatment with platinum.

††The patients had metastatic breast cancer and lymphoma and had previously received large doses of other chemotherapeutic agents.

may occur.[57] Transient myalgia, usually noted two to five days after therapy, is also common at doses above 170 mg per square meter, and myopathy has been noted with high doses of paclitaxel (>250 mg per square meter) in combination with cisplatin.[56,58]

Cardiac Effects

Paclitaxel causes disturbances in cardiac rhythm, but the importance of these effects is not known.[59-61] The most common effect, a transient asymptomatic bradycardia, was noted in 29 percent of patients in one trial.[50] Isolated asymptomatic bradycardia without hemodynamic effects is not an indication for discontinuing paclitaxel. More important bradyarrhythmias, including Mobitz type I (Wenckebach's syndrome), Mobitz type II, and third-degree heart block, have also been noted,[50,59-61] but the incidence in a large National Cancer Institute data base was only 0.1 percent.[61] All events occurred in patients enrolled in trials that required continuous cardiac monitoring, indicating that second- and third-degree heart block is probably underreported, since continuous cardiac monitoring is not usually performed. Most documented episodes have been asymptomatic and reversible. These bradyarrhythmias are probably caused by paclitaxel, since related taxanes affect cardiac automaticity and conduction and since similar disturbances have occurred in humans and animals that had ingested various species of yew plants.[61]

Myocardial infarction, cardiac ischemia, atrial arrhythmias, and ventricular tachycardia have also been noted.[50,59-61] Whether there is a direct causal relation between paclitaxel and ventricular and atrial tachycardias, or between paclitaxel and ischemic events, is uncertain.[61] There is also no evidence of cumulative toxicity or augmentation of the acute cardiac effects of the anthracyclines[61]; however, the frequency of congestive cardiotoxicity in patients treated with paclitaxel and doxorubicin in one trial was higher than expected from the latter alone.[62] In patients treated with paclitaxel and an anthracycline, potential drug effects on ventricular function should be evaluated at lower cumulative anthracycline doses than might otherwise be done with an anthracycline alone.

Once cardiac effects were documented, eligibility in most trials was restricted to patients with no history of cardiac disease. However, this broadly described population undoubtedly excludes many patients who might otherwise be good candidates for paclitaxel, and the risk of cardiotoxicity in patients with cardiac disease is not known. Cardiac monitoring during paclitaxel therapy is not necessary routinely but is advisable for patients who may not be able to tolerate the drug's potential bradyarrhythmic effects, such as those with atrioventricular conduction defects or ventricular dysfunction.

Miscellaneous Toxic Effects

Drug-related gastrointestinal effects of paclitaxel use, such as vomiting and diarrhea, are infrequent.[41] Higher doses may cause mucositis, especially in patients with leukemia who may be more prone to breakdown of the

mucosal barrier[20,37] or in patients receiving 96-hour infusions.[41] Rare cases of neutropenic enterocolitis have occurred, particularly in patients given high doses of paclitaxel in combination with doxorubicin or cyclophosphamide.[63,64] Like other chemotherapeutic agents, paclitaxel induces reversible alopecia of the scalp, and all body hair is often lost with cumulative therapy. Inflammation at the injection site, along the course of an injected vein, and in areas of drug extravasation may occur rarely, as may inflammatory skin reactions over previously radiated sites.[41,65,66]

Clinical Pharmacology

Pharmacokinetic data for paclitaxel are shown in Table 2. The clearance of the drug appeared to be linear in early studies of prolonged infusions,[33-35,67,69] but clearance may be nonlinear or saturable when the drug is infused for shorter periods, with both peak plasma concentrations and drug exposure increasing disproportionately with increasing doses.[58,68-70] The peak plasma concentrations in patients assigned to all regimens have been in the range capable of inducing relevant biologic effects in vitro. Despite extensive binding to plasma proteins (95 to 98 percent), paclitaxel is readily cleared from plasma. The volume of distribution is large, suggesting binding to cellular proteins, possibly tubulin. Renal clearance accounts for a small proportion (1 to 8 percent) of total clearance, and therefore dose modifications do not appear to be necessary in patients with renal dysfunction.[33-35,67,69,71] Hepatic metabolism, biliary excretion, fecal elimination, or extensive tissue binding appears to be responsible for most of the systemic clearance.[69,72,73] The biliary concentrations of both paclitaxel and its hydroxylated metabolites, formed by cytochrome P-450 enzyme systems, are high.[72-75] The optimal dose for patients with hepatic dysfunction has not been determined, nor has the potential for interactions with drugs that may modulate the activity of hepatic P-450 enzymes. On the basis of available data, the doses of paclitaxel should be reduced by at least 50 percent in patients with moderate or severe hyperbilirubinemia or substantially increased serum aminotransferase concentrations.[76]

As part of the effort to combine paclitaxel with cisplatin after prominent single-agent activity was noted in women with advanced ovarian cancer, the possibility of sequence-dependent drug interactions was studied.[59] The principal toxic effect, neutropenia, was more severe when cisplatin was administered before paclitaxel. This appeared to be due to decreased plasma clearance of paclitaxel after cisplatin, possibly caused by the modulating effects of cisplatin on cytochrome P-450 enzymes.[73,77] The less toxic sequence — paclitaxel followed by cisplatin — was more cytotoxic to tumor cells in vitro.[78] These findings formed the rationale for using paclitaxel followed by cisplatin in trials of combination therapy.[79] Important sequence-dependent interactions have also been identified in studies of paclitaxel–doxorubicin and paclitaxel–cyclophosphamide regimens.[64,80]

Antitumor Activity

Ovarian Cancer

Paclitaxel was initially approved by the Food and Drug Administration in 1992 for treating women with epithelial ovarian cancer on the basis of the results of trials of 24-hour infusions of paclitaxel alone (Table 3).[38,50,54,81,82] These results provided the impetus for broad phase 2 testing. In the first study, 30 percent of a group of heavily pretreated women had major antitumor responses. A major response was defined as either a complete response (the complete disappearance of all disease, with normalization of tumor markers) or a partial response (a reduction in the sum of the products of the bidimensional measurements of all known sites of disease by at least 50 percent).[50] The durations of response ranged from 1 to 15 months, with a median of 6 months. Twenty-four percent of the women considered resistant to platinum-based therapy (those who had disease progression within six months) responded, whereas 40 percent of those who relapsed more than

Table 2. Pharmacokinetic Properties of Paclitaxel.*

Duration of Infusion	Model	Half-life			CL	VD_{ss}	C_{peak}	Study
		alpha	beta	gamma				
			hours		*ml/min/m²*	*liter/m²*	*μmol/liter (dose)*	
3 hr	Triphasic	0.20	1.4	14.4	294	98	2.5 (135 mg/m²)	Huizing et al.[52]
	Saturable	0.27	2.3	18.8	212	99	4.3 (175 mg/m²)	
6 hr	Biphasic	0.36	6.4	—	195	59	2.2–13.0 (170–275 mg/m²)	Brown et al.,[33] Wiernik et al.,[34] Longnecker et al.[67]
24 hr	Biphasic	0.39	3.3	—	359	119	0.6–0.9 (200–275 mg/m²)	Wiernik et al.[35]
24 hr	Triphasic	0.09	2.2	49.8	363	657	0.2 (135 mg/m²)	Huizing et al.[52]
	Saturable	0.14	2.0	23.6	393	269	0.4 (175 mg/m²)	
24 hr	Saturable elimination and distribution				161†		(<400 mg/m²)	Sonnichsen et al.[68]
					123†		(>400 mg/m²)	
24 hr							0.2–3.4 (110–390 mg/m²)	Rowinsky et al.[20]
96 hr					437		0.05–0.08 (120–160 mg/m²)	Wilson et al.[39]

*Mean values are given. CL denotes systemic clearance, VD_{ss} volume of distribution at steady state, and C_{peak} peak plasma concentration.

†Values are taken from a pediatric study demonstrating saturable pharmacokinetics. Clearance values listed are for doses below 400 mg/m² (161 ml/min/m²) and doses above 400 mg/m² (123 ml/min/m²).

Table 3. Early Evaluations of Paclitaxel in Women with Advanced and Refractory Ovarian Carcinoma.*

Study	No. of Patients	Major Responses†			Response Rate‡	
		Complete	Partial	Overall	Platinum-sensitive	Platinum-resistant
		number		%	*no. with response/total no. (%)*	
Phase 2 single-agent studies						
McGuire et al.[50]	40	1§	11	30	6/15 (40)	6/25 (24)
Thigpen et al.[54]	43	8	8	37	7/16 (44)	9/27 (33)
Einzig et al.[81]	30	1§	5	20	3/NA¶	3/NA¶‖
Phase 1 study of paclitaxel + G-CSF						
Sarosy et al.[38]	14	1	4	36	0/3	5/11 (45)
Phase 2 study of paclitaxel + G-CSF						
Kohn et al.[82]	44	6	15	48	NA¶‖	NA¶‖
All studies	171	17	43	35	13/34 (38)¶	20/63 (32)¶
Treatment referral center program**						
Trimble et al.[55]	652	23	118	22	—	141/652 (22)

*NA denotes not available, and G-CSF granulocyte colony-stimulating factor.

†A complete response is defined as the complete disappearance of tumor present before treatment. A partial response is defined as a reduction by at least 50 percent in the sum of the bidimensional measurements of all known sites of disease.

‡Response rate is defined as the percentage of patients who could be evaluated who had either complete or partial responses. Platinum resistance is defined as tumor progression while receiving or within six months after completing therapy with a platinum-containing chemotherapy regimen.

§Value represents pathologically verified complete responses.

¶These totals do not include previous platinum-response data from the Einstein Medical Center and National Cancer Institute phase 2 studies since this information was not provided in the original reports.[81,82]

‖These specific data were not provided in the original reports.[81,82] Eighty-nine percent of all patients participating in the National Cancer Institute phase 2 study of paclitaxel and G-CSF had platinum-resistant ovarian cancer.[82]

**This is an open-enrollment program permitting compassionate use of paclitaxel in patients with resistance to platinum.

six months after receiving platinum therapy (and who might have responded to repeated platinum therapy) responded. The doses of paclitaxel (110 to 135 mg per square meter) were substantially lower than those that can be safely given to patients who have previously received less extensive therapy. Although severe neutropenia occurred during most courses, even at relatively low doses, it was short-lived and rarely associated with fever. The results of confirmatory trials were similar.[54,81] These results were substantially better than those of other salvage chemotherapies and comparable to the early results with cisplatin.[83,84]

On the basis of encouraging results with relatively low doses of paclitaxel in women with advanced disease, the potential of granulocyte colony-stimulating factor to permit dose escalation was evaluated.[38,82] Major antitumor responses occurred in 48 percent of heavily pretreated patients. The median survival time was 11.5 months, similar to that reported in previous trials using lower doses. The median relapse-free survival time was 6.2 months, and the relapse-free survival rate was 41 percent at 9 months. These results with higher doses suggested the possibility of a relation between the dose of paclitaxel and the response.

The generalizability of the results of clinical trials to the treatment of women with advanced ovarian cancer in general oncology practice was demonstrated in a treatment-referral-center program instituted by the National Cancer Institute.[55] Through this program, paclitaxel (135 mg per square meter over a period of 24 hours) was initially provided to women whose ovarian cancers had progressed after treatment with three regimens. Twenty-two percent of the first 1000 patients had major responses despite their poor prognostic characteristics.

With the demonstration that paclitaxel and cisplatin could be safely combined,[59] a next logical step was to compare paclitaxel (135 mg per square meter) followed by cisplatin (75 mg per square meter) with a standard regimen of cyclophosphamide (750 mg per square meter) and cisplatin (75 mg per square meter) in untreated women with stage III or IV ovarian cancer that had been surgically debulked suboptimally.[79,85] There were major responses in 64 and 77 percent of the women in the cyclophosphamide and paclitaxel groups, respectively ($P = 0.025$), and paclitaxel was associated with a small improvement in surgically defined complete responses (26 percent, as compared with 19 percent; $P = 0.08$). The paclitaxel regimen reduced the risk of recurrence by 32 percent, and the median duration of progression-free survival was 13.8 and 17.9 months for women receiving cyclophosphamide and paclitaxel, respectively; however, the duration of follow-up was too short to permit the assessment of overall survival. Although the incidence of severe neutropenia was higher in the paclitaxel arm, there was no increase in sepsis. This study suggests that the combination of paclitaxel and cisplatin will become the new standard therapy for advanced ovarian cancer.

Two important issues — whether the schedule of administration of paclitaxel (short vs. long infusion) is important from either a toxicologic or a therapeutic standpoint and whether there is a dose–response relation in the usual dosing range — are being studied in women with ovarian cancer. As previously discussed, the effects of two paclitaxel doses (135 and 175 mg per square meter) and two schedules (24-hour and 3-hour infusions) with premedication for hypersensitivity reactions were similar.[45] 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. Although regulatory approval was originally granted for the use of paclitaxel at a dose of 135 mg per square meter on a 24-hour schedule in women with drug-refractory and recurrent ovarian cancer, these results were the impetus for the subsequent approval of doses of 175 mg per square meter of paclitaxel administered

over a period of 3 hours for this indication. The dose–response issue is being assessed in an ongoing trial in which women with platinum-resistant cancers are treated with one of three paclitaxel doses — 135, 175, or 250 mg per square meter (plus granulocyte colony-stimulating factor) given over a period of 24 hours. Two other important trials in women with ovarian cancer are under way. In one trial, women with suboptimally debulked stage III or IV disease are being treated either with a combination of paclitaxel and cisplatin or with maximally tolerated doses of either cisplatin or paclitaxel as single agents to determine whether the combination is more effective than the individual drugs. In the other study, women with stage III disease who have had optimal debulking surgery are being treated with paclitaxel and cisplatin, cyclophosphamide and cisplatin, or paclitaxel and intensive therapy with both cisplatin and carboplatin. Although the cyclophosphamide-and-cisplatin arm has been discontinued because the regimen's activity in patients with suboptimally debulked disease is inferior to that of paclitaxel and cisplatin, the study will provide an opportunity to judge the benefits of paclitaxel in a group of patients with more favorable prognoses.

Table 4. Early Evaluations of Paclitaxel in Metastatic Breast Cancer.

Study	Regimen*	No. of Patients	Major Responses†		Response Rate‡
			Complete	Partial	
			number		%
Holmes et al.[51]	200–250 mg/m² in a 24-hr infusion§	25	3	11	56
Reichman et al.[86]	250 mg/m² in a 24-hr infusion + G-CSF¶	26	2	14	62
Seidman et al.[87]	250 mg/m² in a 24-hr infusion + G-CSF	21‖	2	6	38
	200 mg/m² in a 24-hr infusion + G-CSF	22**		7	32
	200 mg/m² in a 24-hr infusion + G-CSF	29††		5	17
Gelmon et al.[88]	135 mg/m² in a 3-hr infusion‡‡	229	5	46	22
	175 mg/m² in a 3-hr infusion‡‡	225	12	53	29

*Treatment was repeated every three weeks and was continued until tumor progression in all studies except that by Gelmon et al.[88] Because of a limited drug supply at the time of that trial, treatment was continued for 2 courses beyond the best response or until a maximum of 10 courses had been given, unless the tumor was still decreasing in size. G-CSF denotes granulocyte colony-stimulating factor.

†A complete response is defined as the complete disappearance of tumor present before treatment. A partial response is defined as a reduction by at least 50 percent in the sum of the bidimensional measurements of all known sites of disease.

‡Response rate is defined as the percentage of patients who could be evaluated who had either complete or partial responses.

§All patients had received one prior regimen of chemotherapy — 14 as adjuvant therapy and 11 as therapy for metastatic disease. Treatment was continued until the disease progressed.

¶Sixteen patients had received adjuvant therapy only; six patients had received doxorubicin. Because of the limited supply of paclitaxel at the time of the trial, the patients received 2 additional courses after their maximal response or a maximum of 10 courses unless their disease was still regressing. Thus, the duration of response and survival cannot be accurately assessed.

‖All patients had received one regimen of chemotherapy for metastatic disease.

**All patients had received two regimens of chemotherapy for metastatic disease.

††All patients had received at least three regimens of chemotherapy for metastatic disease.

‡‡This was a randomized trial consisting of patients who had previously received either adjuvant therapy only, one regimen for metastatic disease, or adjuvant therapy plus one regimen for metastatic disease.

Breast Cancer

Substantial antitumor activity in women with metastatic breast cancer was originally demonstrated for paclitaxel administered on a 24-hour schedule (Table 4).[51,86] Among 25 women who had received no more than one chemotherapy regimen for metastatic disease, 56 percent had major responses, and the median time to disease progression was nine months.[51] A confirmatory trial in which paclitaxel (250 mg per square meter) was given with granulocyte colony-stimulating factor to women who had previously received either adjuvant therapy only or no prior therapy confirmed this high level of activity[86]; 62 percent had major responses. The likelihood of a major response was not related to either hormonal-receptor status or prior adjuvant therapy. In both trials, responses occurred in all sites of metastases and in cancers that were clearly refractory to anthracyclines.

These encouraging results with paclitaxel in women with metastatic breast cancer are comparable to results reported in early studies of the anthracyclines, which are among the most active agents in breast cancer. Gauging the overall importance of these results and predicting the ultimate role of paclitaxel in breast cancer, a relatively responsive tumor, was difficult, however, since these initial studies were performed in women who had received little prior therapy, unlike the women with ovarian cancer who have been studied. Subsequent studies in more heavily pretreated women have confirmed the initial results,[87,89] although the likelihood of a response is lower in women who have received much previous therapy.[87] Major-response rates have ranged from 38 percent in women previously treated with one regimen for metastatic disease to 17 percent in those previously treated with three or more regimens for metastatic disease.[87] The overall major-response rates in women who are sensitive to anthracyclines or resistant to them are similar.[87,88] This lack of complete cross-resistance between paclitaxel and the anthracyclines suggests that multidrug resistance may not be as important as was originally anticipated in conferring clinical resistance to paclitaxel, at least in women with breast cancer.

Further development of paclitaxel for the treatment of women with breast cancer will involve defining its role in progressively earlier stages of disease and ultimately in adjuvant therapy. In a series of clinical trials, the Eastern Cooperative Oncology Group is treating previously untreated women who have metastatic breast cancer with either paclitaxel or doxorubicin, or both. If paclitaxel-based therapy proves superior, it will be incorporated into adjuvant trials. Intensive sequential chemotherapy with doxorubicin followed by paclitaxel and then cyclophosphamide is being evaluated in the adjuvant treatment of high-risk patients after definitive

management of the primary tumor with surgery and radiation.[90] The usefulness of paclitaxel as part of the adjuvant treatment of high-risk patients is also being studied in a multicenter trial of high, moderate, and low doses of doxorubicin and cyclophosphamide followed either by paclitaxel and then tamoxifen or by tamoxifen alone.

Optimal dosing and scheduling of paclitaxel are being evaluated in women with metastatic breast cancer. Early results of a European trial of three-hour infusions of paclitaxel at 135 or 175 mg per square meter indicate no significant differences in response rates (29 percent [high dose] vs. 22 percent [low dose]) or in median survival (11.7 months [high dose] vs. 10.5 months [low dose]).[88] There was also no difference in response rates between women with resistance to anthracycline therapy and those without such resistance. The results of this trial, as well as of previous phase 2 trials, led to regulatory approval of paclitaxel at a dose of 175 mg per square meter over a period of three hours for the treatment of metastatic breast cancer after failure of combination chemotherapy or relapse within six months of adjuvant chemotherapy. A multicenter trial in the United States of women who have undergone one chemotherapy regimen for metastic breast cancer or who relapsed after adjuvant therapy is also addressing optimal dosing, with doses of 175, 210, and 250 mg per square meter. Optimal drug scheduling is also being addressed in a trial in which women who have not received chemotherapy are being treated with either 3-hour or 24-hour infusions of paclitaxel (250 mg per square meter) with granulocyte colony-stimulating factor.

Table 5. Phase 2 Studies of Paclitaxel in Advanced Lung Cancer.

Study	Regimen*	No. of Patients	Major Responses†		Response Rate‡
			complete	partial	
			number		%
Non–small cell					
Murphy et al.[91]	200 mg/m² in a 24-hr infusion§	25	1	5	24
Chang et al.[92]	250 mg/m² in a 24-hr infusion¶	24	0	5	21
Small cell‖					
Ettinger et al.[93]	250 mg/m² in a 24-hr infusion**	34	—	11–14††	32–41††
Kirschling et al.[94]	250 mg/m² in a 24-hr infusion + G-CSF‡‡	37	—	15	41

*G-CSF denotes granulocyte colony-stimulating factor. Treatment was repeated every three weeks in all studies.

†A complete response is defined as the complete disappearance of tumor present before treatment. A partial response is defined as a reduction by at least 50 percent in the sum of the bidimensional measurements of all known sites of disease.

‡Response rate is defined as the percentage of patients who could be evaluated who had either complete or partial responses.

§Patients with stable disease received only three courses. Patients with complete responses received two additional courses, whereas those with lesser degrees of response were treated until tumor progression.

¶Patients were treated until the disease progressed.

‖Only patients with extensive small-cell carcinomas were eligible.

**Treatment was continued unless patients had tumor progression after one course of paclitaxel, had stable disease after two courses, or had only a partial response after four courses.

††Three patients who had tumor reductions greater than 50 percent were not formally considered to have partial responses because they underwent salvage chemotherapy and did not have a second confirmatory measurement performed.

‡‡Patients were treated until the tumor progressed.

Lung Cancer

Paclitaxel has also been evaluated in previously untreated patients with advanced non–small-cell lung cancer, at high starting doses (200 to 250 mg per square meter) with 24-hour infusions (Table 5).[91,92] In one study, the major-response rate was 24 percent, the median duration of response was 27 weeks, and median survival was 40 weeks (56 weeks for those who responded to treatment).[91] In a randomized phase 2 study that also included the investigational agents piroxantrone and merbarone, major-response rates were 21, 2.3, and 0 percent for paclitaxel, piroxantrone, and merbarone, respectively. The median duration of response to paclitaxel was 6.5 months, the 1-year survival rate was 41.7 percent, and median survival was 24.1 weeks.[92] In two other studies, the major-response rates in untreated patients with extensive small-cell lung cancer who were given paclitaxel (250 mg per square meter) with and without granulocyte colony-stimulating factor were 41 and 34 percent, respectively (Table 5),[93,94] results that compare favorably with those for any other single agent used against this tumor.

The next trials in lung cancer will evaluate the efficacy of combination chemotherapy. Two regimens of standard therapy are being compared in previously untreated patients with metastatic non–small-cell lung cancer. One consists of etoposide (100 mg per square meter) on days 1 to 3 and cisplatin (75 mg per square meter); the other consists of cisplatin (75 mg per square meter) and 24-hour infusions of paclitaxel given at either low or high doses (135 or 250 mg per square meter) with granulocyte colony-stimulating factor.

Head and Neck Cancer

Paclitaxel (250 mg per square meter for 24 hours with granulocyte colony-stimulating factor) has demonstrated activity in patients with locally recurrent and metastatic squamous-cell carcinoma of the head and neck who have received no prior chemotherapy. In a multicenter phase 2 trial, 43 percent of patients had major responses, a result that compares favorably with the response rate achieved with any single conventional agent.[95] The role of different dosage levels of paclitaxel and the efficacy of various schedules of the drug in combination with other active drugs, such as cisplatin, fluorouracil, or ifosfamide, are currently being investigated.

Other Tumor Types

Although paclitaxel was active in melanoma in preclinical studies and several patients had responses in phase 1 trials, response rates were only 12 and 18 per-

cent in phase 2 studies.[96,97] Phase 2 trials in prostate, colorectal, renal, pancreatic, and gastric cancers were also negative.[98-102] The major-response rate was also low (17 percent) in patients with relapsed non-Hodgkin's lymphoma.[103] In another study, 14 and 29 percent of patients with primary refractory and relapsed non-Hodgkin's lymphoma, respectively, responded to paclitaxel.[104] In contrast, paclitaxel (250 mg per square meter) for 24 hours with granulocyte colony-stimulating factor has had beneficial effects on patients with testicular, bladder, or esophageal cancer.[105-107] Forty-two percent of the untreated patients with advanced transitional-cell carcinoma of the bladder had major responses.[105] The major-response rate in patients with advanced esophageal cancer was 32 percent, despite a low level of activity in other gastrointestinal cancers; responses occurred in both adenocarcinoma (34 percent) and squamous-cell carcinoma (28 percent) subtypes.[106] In addition, 24 percent of patients with cisplatin-resistant germ-cell cancer had major responses in one study.[107]

Future Directions

The methods used to assess the anticancer activity of paclitaxel represent a departure from the traditional methods used to evaluate new anticancer agents, in that high doses (250 mg per square meter for 24 hours) and occasionally hematopoietic growth factors were used in most early studies and a greater degree of neutropenia was accepted. The reason for these departures is that the supply of drug when phase 2 testing began was limited, and it was thought that the use of high starting doses would obviate the repetition of studies at high doses if results were equivocal with low doses. Since high doses of paclitaxel have not been established to be superior to low doses, studies comparing high and low doses are warranted in tumors against which the drug is active.

Building on the encouraging results with paclitaxel has required finding a long-term solution to the drug-supply problem. The limited supply of paclitaxel has stimulated extensive collaborations between private industry and government. In 1989, after an open competition initiated by the National Cancer Institute, a Collaborative Research and Development Award was given to Bristol-Myers Squibb to develop and market paclitaxel. The award also stipulated that Bristol-Myers Squibb organize research and develop alternative drug sources. Until recently, drug supplies came from tree bark, but in the future they will be derived increasingly from parts of the tree other than bark, semisynthetic materials, cultivated ornamental taxus species, and plant-tissue cultures. Paclitaxel can now be made by a partially synthetic process that has been scaled up to produce sufficient quantities of drug to meet projected future demands.[108] This process uses a readily available precursor, 10-deacetylbaccatin III, derived from the needles of more abundant yew species. At least two totally synthetic methods have been described, but their inefficiency precludes their use at this time.[109-111]

Another approach to the development of the taxanes includes the identification of analogues through structure–function studies. One such analogue, docetaxel (Taxotere), is synthesized from 10-deacetylbaccatin III.[102,108,112,113] As with paclitaxel, the principal toxic effect of docetaxel is neutropenia. Hypersensitivity reactions have also been noted, and premedication is now widely used. Unique toxic effects include a maculopapular rash with occasional bullous features, and with cumulative therapy, peripheral edema and pleural effusions that resemble a capillary-leak syndrome and often result in the discontinuation of treatment. Substantial antitumor activity has been noted in patients with non–small-cell lung, breast, ovarian, and pancreatic cancers, and methods of preventing fluid retention are being investigated.[114-119]

The recognition of the novel mechanism of action and the clinical usefulness of the taxanes has increased our appreciation of the microtubule as a target for anticancer drugs. The results with paclitaxel have stimulated renewed interest in the development of not only the taxanes but also other natural products. The results of ongoing investigations will undoubtedly reveal the magnitude of the potential role of the taxanes in oncologic therapeutics.

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