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Review paper

Taxol: a new and effective anti-cancer drug

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Taxol is a new anti-cancer drug that is a natural product derived from the bark of the Pacific Yew tree. The drug promotes polymerization and stabilization of tubulin to microtubules and interferes with the mitotic spindle. Clinical trials indicate that taxol is effective in the treatment of patients with refractory ovarian cancer, breast cancer, malignant melanoma and probably other solid tumors. Toxicities include anaphylactoid reactions, leukopenia, peripheral neuropathy and oropharyngeal mucositis. Increased supplies of the drug are required to support further phase II and III testing.

Key words: Breast cancer, cancer chemotherapy, microtubules, natural products, ovarian cancer, taxol.

Introduction

This article reviews the preclinical and clinical experience with taxol, a new anti-neoplastic drug. It has a novel mechanism of action, efficacy for some patients who have failed other therapies and unexplored potential for combined use with other anti-cancer drugs. It is a natural product derived from an evergreen tree. Taxol promotes the formation of microtubules and inhibits their normal disassembly. Though it remains untested against many specific neoplasms, taxol has elicited clinical responses for patients with malignant melanoma, breast cancer and drug-refractory ovarian cancer. The toxicities and pharmacokinetics of taxol have been described. Although supplies of the drug are currently limited, taxol appears to be a promising anti-neoplastic drug. Further clinical experience will better define the spectrum of activity for taxol and clarify its role in combination chemotherapy.

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Drug information

Biochemistry

Taxol was first identified in the laboratory of Monroe Wall at the Research Triangle Institute in Research Triangle Park, North Carolina in 1971.[1] It was derived from the stem bark of the western yew, *Taxus brevifolia*, which had been shown previously to possess anti-leukemic properties. Important features of the structure are the unusual eight-membered taxane ring and the bulky side chain at the C-13 position (see Figures 1 and 2).

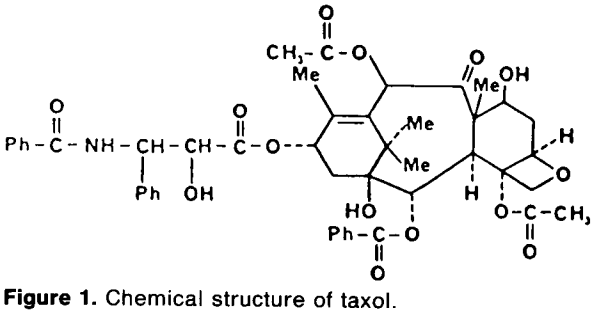

Figure 1. Chemical structure of taxol.

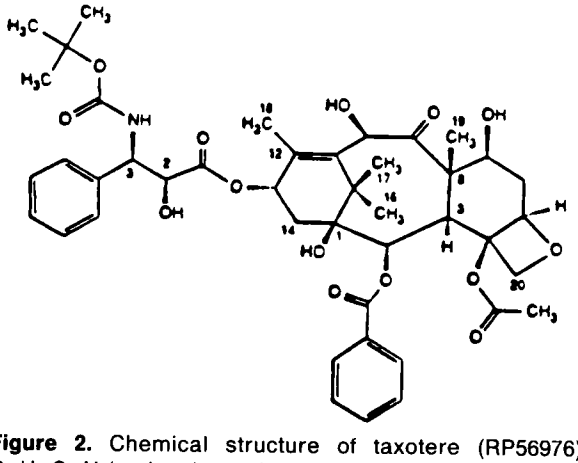

Figure 2. Chemical structure of taxotere (RP56976): $C_{43}H_{53}O_{14}N$ (molecular weight = 807.9).

Taxol is poorly soluble in water. It is slowly converted to the less active molecule 7-epitaxol in cell culture medium,[2] but this is clinically insignificant.[3]

General biologic effects

Because it has been widely used as a pharmacologic probe of microtubule physiology, several effects have been ascribed to taxol at the molecular and cellular levels (see Table 1). Taxol inhibits DNA synthesis,[4,5] motility,[6–11] secretion[12–16] and receptor-mediated processes.[17–19] It produces degenerative and developmental alterations in neural cells and tissues.[20–24] Most of these effects occur at taxol concentrations lower than the peak plasma levels measured in clinical trials (see Table 2). The physiologic or toxic consequences of these phenomena in patients treated with taxol are unknown.

Mechanism of action

Taxol has a novel mechanism of action. It shifts the normal dynamic equilibrium from the monomeric protein tubulin towards its polymerized form, the microtubule. Taxol increases the rate and extent of polymerization and inhibits depolymerization. The drug reversible binds to microtubules at a site distinct from that of colchicine, nocodazole, the vinca alkaloids and podophyllotoxin, all inhibitors of microtubule assembly. These interactions have been reviewed elsewhere.[25,26]

Taxol-induced bundles of microtubules have been identified in a variety of cells and tissues. These are morphologically distinct with the electron microscope[27,28] or with immunofluorescence microscopy.[29] Identification of these immunofluorescent bundles in leukemia cells from patients correlated with clinical response to therapy with taxol and might provide the basis for an assay that predicts clinical responsiveness.[30] Cells that are in mitosis when exposed to taxol form abnormal aster-like structures rather than microtubule bundles.[31]

Paralysis of the mitotic spindle is the best supported explanation for the cytotoxic effects of

Table 1. Some biological effects of taxol

Effect	Reference
Inhibit initiation of DNA synthesis	4, 5
Inhibit cell mortility or migration	6, 7
Inhibit contractility of chorioretinal fibroblasts	8
Inhibit nuclear migration in fertilized sea urchin eggs	9
Inhibit neutrophil function	10, 11
Trigger release of tumor necrosis factor α from macrophages	12
Inhibit hormone-stimulated adrenal steroid production	13
Induce the maturation of hepatic autophagosomes	14
Inhibit hepatocyte protein secretion	15, 16
Inhibit catecholamine release from adrenal chromaffin cells	17, 18
Inhibit mitogen-stimulated lymphocyte proliferation	19
Inhibition of initiation and branching of chick neurites	20, 21
Distal degeneration of axons	22–24

Table 2. Some reported concentrations and effects of taxol

Taxol molarity	Effect	Reference
3×10^{-9}	IC_{50}[a] for rabbit chorioretinal fibroblasts	8
1×10^{-8}	cytotoxic for prostrate carcinoma cells with prolonged exposure	56
1×10^{-7}	diminished PMN Chemotaxis	11
	more than 75% of human leukemia HL60 cells demonstrate microtubule bundles	29
	approximate IC_{50} for sensitive human leukemia lines	29
3×10^{-7}	diminished thrombin-induced DNA synthesis in mouse embryo cells	4
1×10^{-6}	microtubule bundles observed in neurons of mouse dorsal-root ganglia	27
3×10^{-6}	average peak concentration in human serum in phase I clinical trials	3, 30
1×10^{-5}	highest peak concentrations in human serum in phase I trials	52, 55
	diminished production and release of steroid hormones from adrenocortical cells	13
	diminished PMN killing of *Staphylococcus aureus*	11
5×10^{-5}	IC_{50} for resistant cell line J774.2/TAX50	25

[a] IC_{50} indicates concentration of taxol which inhibits cell growth by 50%.

taxol. Normal mitotic anaphase requires microtubule disassembly at the kinetochore, the site of attachment of the chromosomes to the mitotic spindle.[32] Taxol prevents microtubule disassembly, and chromosomal non-disjunction has been observed.[33–35] Mitotic arrest was described in biopsy and autopsy specimens from a variety of organs from patients treated with taxol.[36]

Mechanisms of resistance

Several mechanisms of resistance to the cytotoxic effects of taxol have been described. A membrane glycoprotein has been isolated from cell lines made resistant to multiple drugs by passage through increasing concentrations of taxol.[25] This glycoprotein is probably related to P-glycoprotein, a known mediator of multiple drug resistance.[37] Resistance to taxol has been observed in other multiply-resistant cell lines.[38,39] Some taxol-resistant cell lines have acquired mutant tubulins which are highly sensitive to the cytotoxic effects of microtubule destablizing drugs.[40,41] This observation suggests that alternating taxol with a non-cross resistant agent may be a successful clinical strategy.

Polyploidization[42] and reversibility of microtubule bundling[30] in leukemic blasts correlated with resistance to taxol. The clinical significance of these observations is unknown.

Preclinical data

Taxol is effective in killing HeLa and BALB/c cell lines.[43] Good activity was noted against intraperitoneal B16 melanoma and MX-1 mammary carcinoma implanted in the renal capsule of nude mice.[43] Moderate activity was found against i.p. L1210, P388 leukemia models, CX-1 colon and LX-1 lung carcinomas.[43] No activity was seen against subcutaneous models of CD8F1 mammary carcinoma, colon 38 or Lewis lung carcinoma.[43] Treatment of L1210 leukemia cells resistant to both taxol and vincristine with either of these drugs followed or preceded by cisplatin demonstrated the greatest cytotoxic effects occurred when taxol preceded cisplatin.[44] Testing of human tumors transplanted into animal models has shown good activity against breast, endometrial, ovarian, lung and tongue carcinomas, and against a glioblastoma multiforme.[45] Taxol was ineffective against two transplanted pancreatic carcinomas.[46]

Testing in the human tumor stem cell assay[47] of tumor specimens derived from patients found that 11% of specimens had more than 50% growth inhibition at a taxol concentration of 1.0 μg/ml (peak levels in phase I studies are in the range of 1.0–10.0 μg/ml) and that 32% of specimens had greater than 50% inhibition at 10.00 μg/ml (see Table 3). Tumors responding well in the clonogenic assay include those arising from breast, lung (small cell and non-small cell), melanoma, ovary, prostate and testis (DD Von Hoff, unpublished data). In a related assay, taxol was found to have a favorable cytotoxicity profile relative to standard chemotherapy against 36 varied human tumor specimens when concentrations were controlled for toxic effects on granulocyte-macrophage colony-forming cells[48].

Table 3. Human tumor stem cell assay: effect of taxol concentration upon survival

Concentration		*n*	No. with <50 survival (%)	No. with <30 survival (%)
(μg/ml)	(M × 10^{-6})			
0.10	(0.117)	25	1 (4)	1 (4)
1.0	(1.17)	28	3 (11)	1 (4)
10.0	(11.7)	25	8 (32)	1 (4)

Taxol has also been shown to reduce the incidence and extent of proliferative vitreoretinopathy in animal models, and may be useful in the prevention of retinal detachment.[8] The microtubules of mammals and protozoa are sufficiently dissimilar that taxol or an analogue may prove useful in the treatment of parasitic disease.[49]

Animal toxicology

Toxicity studies in animals were performed under the guidance of the National Cancer Institute in mouse, rat and dog species.[43] Dogs were treated with intravenous taxol, but due to constraints of dose and volume, rodents were given intraperitoneal therapy. In rats and dogs, the major toxicity was dose-related and reversible myelosuppression of neutrophils and lymphocytes. Also common were anemia in dogs and lymphoid depletion in mice. Intestinal inflammation and necrosis were seen in some dogs. Mice developed gastritis and duodenitis. Oligospermia was present in rodents. Cardiovascular collapse was seen in several dogs and was thought to be related to the solvent vehicle. Cremophor has been implicated in similar clinical reactions with other anti-neoplastic

drugs[50] and causes release of histamine when given to dogs.[51]

Clinical pharmacology

Pharmacokinetic parameters have been measured in five clinical trials of taxol.[3,52–55] All have utilized high-pressure chromatography to measure taxol concentrations and employed a biphasic model of clearance. Four of the studies infused taxol over 6 or 24 h and are shown in Table 4. These showed relatively close agreement for several parameters. The terminal half life varied from 3.3 to 8.6 h, the clearance from 134 to 359 ml/min/m^2 and the peak serum concentration was as high as 13 μM. The volume of distribution ranged from 57 to 167 l/m^2, reflecting extensive protein binding. Equilibrium dialysis confirmed this, with approximately 97.5% of taxol protein bound.[54] Between 2.1 and 5.9% of a dose is excreted in the urine. The predominant mode of clearance is probably hepatic, but this is unproven.

Taxol was assayed in ascites of one patient[55] and reached a maximum concentration of 0.25 μM a few hours after completion of the 6 h intravenous infusion. The level remained approximately 40% above the serum concentration for several hours. Taxol was not detected in spinal fluid sampled from one patient at the completion of an infusion.[30]

Clinical responses and some toxicity appear to be dose-related. The area under the plasma disappearance curve correlates roughly with severity of neutropenia.[52] At phase II doses, 6 and 24 h regimens attain peak plasma levels well above the concentrations required for cytotoxicity,[29,56] neural degeneration[89] or microtubule bundling in leukemic blasts[30] (see Table 2).

A pharmacokinetic trial of intraperitoneal taxol has been reported recently.[57] Peak intraperitoneal taxol levels of 19–88 μM were achieved with peak cavity to plasma concentration ratios of 150–800. These data suggest that intraperitoneal administration offers theoretical advantages for patients with intraperitoneal tumors and that this route of delivery deserves further study.[57]

Drug supply and mode of administration

'Taxol' is the brand name of a laxative agent that contains bile salts as the active ingredient. It is no longer in production and should not be confused with the anti-neoplastic agent of the same name.[58]

The anti-cancer drug taxol is supplied as a concentrated sterile solution, 6 mg/ml in 5 ml ampules in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol. The ampules must be diluted with saline or D5W to a final concentration of less than 0.6 mg/ml. The solution is slightly hazy and includes a small number of fibers which requires the use of an in-line filter with all infusions. The drug should be refrigerated prior to use (2–8°C).[43] Glass or polyolefin containers and polyethylene-lined tubing should be used to administer taxol.[58]

Efforts to increase the supply of taxol are underway. This is imperative because the Western Yew is a slow-growing evergreen tree with a limited population indigenous to an ecologically fragile environment in the Pacific Northwest. Extensive efforts to synthesize taxol have not yet succeeded due to the skeletal and stereochemical complexity of the molecule.[59] Baccatin is an abundant plant-derived substance that has been converted to taxol, but the applicability of this method to large-scale production is unproven.[60] Growth of *T. brevifolia* in tissue culture may also provide adequate supplies of taxol in the future.[61] The number and size of clinical trials are currently limited by the availability of taxol.

A more abundant taxol derivative, *N*-debenzoyl-*N*-*tert*-butoxycarbonyl-10-deacetyltaxol (RP 56976), or taxotere, has shown good antitumor efficacy in

Table 4. Clinical pharmacokinetic data studies utilizing continuous infusion

Center[a] (reference)	Infusion time (h)	$T_{1/2B}$ (h)	Clearance (ml/min/m^2)	Peak concentration (M × 10^{-6})	V_d (l/m^2)
JH (52)	1–6	6.4	253	1.3–13.0	67
AE (55)	6	8.6	134	2.0–10.1	57
SA (3)	6	4.3	231	2.4–4.7	49
AE (54)	24	3.3	359	0.5–1.3	119

[a] JH, The Johns Hopkins Oncology Center; SA, University of Texas, San Antonio; AE, Albert Einstein Cancer Center.

animal models.[63,64] One of us (DVH) is participating in the first US clinical trial of taxotere.

Results of clinical trials

This review includes nine phase I clinical trials of taxol alone, one clinical trial of taxol combined with cisplatin and six phase II trials. Phase I trials are designed to define the appropriate dosage and toxicity, and specific conclusions regarding antitumor response rates cannot be drawn. Phase II clinical trials utilize the dose information derived from phase I trials and test the drug in patients with specified cancers. A complete response is total disappearance of clinically detectable tumor for at least 1 month. A partial response is defined as a reduction of total cross-sectional area of tumor of at least 50% and minimum duration 1 month. Minimal response is a measurable reduction of tumor burden that does not meet criteria for complete or partial response. Response rate is the proportion of patients who have a complete or partial response to therapy.

Phase I trials (see Table 5)

One of the first clinical trials with taxol was performed at Memorial Sloan Kettering Cancer Center in New York.[65] Seventeen patients were treated at doses from 15 to 230 mg/m^2. This was administered over 3 h and repeated every 3 weeks as tolerated. Anaphylactoid reactions occurred in three of five patients treated at doses greater than 185 mg/m^2 and one of these died as a result. Mild myelosuppression was observed and no clinical responses were seen.

Anaphylactoid reactions were encountered in another early study from the Johns Hopkins Oncology Center.[66] In an effort to minimize these reactions, the infusion time was increased from 1 to 6 h, and patients were given prednisone, diphenhydramine and cimetidine prior to taxol therapy. On this schedule, leukopenia was the dose-limiting toxicity and the recommended phase II starting doses were 170 and 212 mg/m^2 for patients with minimal and extensive prior chemoradiotherapy, respectively. One patient each with lung adenocarcinoma and ovarian carcinoma improved clinically with this regimen.

Another study encountered anaphylactoid reactions with 1 h infusions.[53] With steroid and anti-histamine pretreatment and a 6 h infusion time the maximum tolerated dose was 150 mg/m^2 divided over 5 days. The dose-limiting toxicity was leukopenia. No antitumor responses were seen among 16 patients treated.

Leukopenia limited the dose in a study of 1 h infusions given daily for 5 days.[68] The recommended phase II starting dose was 150 mg/m^2 over 5 days. No responses were seen.

One of us (DVH) has investigated the use of a 6 h infusion without premedication and found myelosuppression to be the dose-limiting toxicity. A single patient had a hypersensitivity reaction and she did well when her infusion was stopped, she was treated with steroids and anti-histamines, and her taxol was continued. The maximum tolerated dose was 275 mg/m^2 and the recommended phase

Table 5. Taxol phase I clinical trials

Dose schedule	Infusion duration (h)	Recommended phase II dose (mg/m^2)	Dose-limiting toxicity	Center[a] (reference)
Once every 3 weeks	3	NR[b]	hypersensitivity	MSK (65)
Once every 3 weeks	1	NR[b]	hypersensitivity	JH (66)
Once every 3 weeks	6	212[c]	leukopenia	JH (66)
Daily a q 4 weeks	1	NR[b]	hypersensitivity	WCC (53)
Daily × 5 q 4 weeks	6	30 × 5 days	leukopenia	WCC (53)
Daily × 5 q 3 weeks	1	30 × 5 days	leukopenia	MDA (67)
Once every 3 weeks	6	225	myelosuppression	SA (3)
Once every 3 weeks	6	250	neuro/leukopenia	AE (55)
Once every 3 weeks	24	170	leukopenia	MSS (68)
Once every 3 weeks	24	250	neuropathy	AE (54)
Once every 2–3 weeks	4	315	mucositis	JH (30)

[a] MSK, Memorial Sloan Kettering Cancer Center; JH, The Johns Hopkins Oncology Center; WCC, Wisconsin Cancer Center; MDA, MD Anderson Cancer Center; SA, University of Texas, San Antonio; AE, Albert Einstein Cancer Center, MSS, Mount Sinai School of Medicine.
[b] Not recommended.
[c] Lower dose suggested for patients with extensive prior therapy.

II dose 225 mg/m^2. Partial responses were seen in a patient with squamous cell carcinoma of lung and another patient with adenocarcinoma of unknown primary.[3]

Minor responses were seen in patients with gastric and ovarian carcinoma in another study using 6 h infusions.[55] Anaphylactoid reactions were a problem in four of the first 13 courses and premedications were added for the remaining seventy courses. The recommended phase II starting dose was 250 mg/m^2. Peripheral neuropathy and leukopenia were the dose-limiting toxicities.

Peripheral neuropathy was also encountered with taxol administered by 24 h continuous infusion. Neutropenia was significant. Partial responses were seen in four of 12 patients with melanoma. The recommended phase II starting dose was 250 mg/m^2.[54]

Another study using the 24 h continuous infusion schedule found leukopenia to be the dose-limiting toxicity.[68] The recommended phase II starting dose was 170 mg/m^2. Minimal improvement was seen in two patients.

In a phase I–II study of patients with refractory acute leukemia, mucositis was the dose-limiting toxicity using a 24 h infusion.[30] The maximum tolerated dose was 390 mg/m^2 and the recommended phase II dose 315 mg/m^2. Three of 17 patients had complete clearance of blasts from the marrow.

An ongoing phase I study combines taxol and cisplatinum.[69] Twenty-five patients with minimal prior therapy received 75 courses starting at the minimal toxic doses for each drug, 50 mg/m^2 for cisplatin and 110 mg/m^2 for taxol. Neurotoxicity was anticipated but has not been clinically significant at doses reported in preliminary findings from this study.[69] The dose-limiting toxicity has been neutropenia, and the investigators plan to escalate the doses further with concurrent use of leukocyte colony-stimulating factors (WP McGuire, personal communication).

These phase I studies have pointed the way for future investigation. The doses recommended for phase II testing vary from 170 mg/m^2 over 24 h[68] to 250 mg/m^2 over 6 or 24 h.[54,55] For patients with leukemia, 315 mg/m^2 over 24 h is recommended for phase II testing.[30] Because prior chemotherapy and radiotherapy sensitizes a patient to the myelotoxic effects of taxol, another author recommends a 6 h infusion of 212 or 170 mg/m^2, depending upon the degree of prior treatment.[66] Only prospective, randomized clinical trials can demonstrate what schedules of administration are most effective in the treatment of specific malignancies.

Sporadic clinical improvement or responses for patients with a variety of neoplasms were reported during phase I testing, including acute lymphocytic and myelocytic leukemia,[30] lung adenocarcinoma,[3,66] lung squamous carcinoma[3] adenocarcinoma of unknown primary,[3,55] colon carcinoma,[55,68] metastatic gastric cancer,[55] and head and neck carcinoma.[68]

Phase II clinical trials (see Table 6)

Taxol has shown impressive activity in the treatment of patients with ovarian cancer. This was first observed in phase I trials[55,66] and has been confirmed in phase II studies. In the first of these, McGuire *et al.* treated patients who were refractory to prior therapy.[70] Before the introduction of taxol, salvage chemotherapy for these patients had met with an overall response rate of 6%.[71] Taxol improved the response rate to 30% when 110–250 mg/m^2 was given over a 24 h period.[70]

Table 6. Response rates in phase II clinical trials of taxol

Primary tumor	Evaluable patients	CR (%)	PR (%)	Overall response rate (%)	Center[a] (reference)
Ovary	40	1 (3)	11 (28)	30	JH (70)
Ovary	29	1 (3)	5 (17)	21	AE (72)
Ovary	41	5 (12)	10 (24)	37	GOG (73)
Melanoma	28	3 (11)	1 (4)	14	AE (75)
Melanoma	25	0 (0)	3 (12)	12	MDA (76)
Breast	25	3 (12)	9 (36)	48	MDA (74)
Renal	18	0 (0)	0 (0)	0	AE (77)

[a] JH, The John Hopkins Oncology Center; AE, Albert Einstein Cancer Center; GOG, Gynecologic Oncology Group; MDA, MD Anderson Cancer Center. CR = complete response; PR = partial response.

These patients were given dexamethasone, diphenhydramine and ranitidine prior to the taxol infusion. Courses were repeated every 3 weeks as tolerated. Of 47 evaluable patients, one had a complete response and 11 had partial responses. Leukopenia was the dose-limiting toxicity, and other adverse effects included myalgias, arthralgias, alopecia, diarrhea, nausea, vomiting, mucositis and peripheral neuropathy.

These important findings were recently confirmed in two other phase II clinical trials for the treatment of patients with ovarian cancer. One of these studies used a regimen similar to McGuire *et al.*'s and obtained one complete response and five partial responses among 29 evaluable patients for an overall response rate of 21%.[72] In the other study, taxol at 175 mg/m^2 was given over 24 h every 3 weeks.[73] Among 41 evaluable patients, five complete and 10 partial responses gave an overall response rate of 37%. The differences in response rates in these two studies do not differ significantly from one another ($0.2 > p > 0.1$). In both of these studies, leukopenia was the most significant toxicity. When pooled with the data from McGuire's group, the overall response rate for ovarian cancer with taxol on this regimen is 30%, with 95% confidence intervals 21.4–38.6%.

A phase II study of patients with metastatic breast cancer obtained a 48% response rate.[74] The 25 patients enabled were started at 250 mg/m^2 of taxol given by 24 h infusion (or 200 mg/m^2 for patients who had limited marrow reserve due to previous therapy). A complete response rate of 12% and partial response rate of 36% were reported with the duration of responses from 1 to 8 months. These encouraging results should stimulate further investigation of the use of taxol for patients with breast cancer.[74]

Two phase II studies of patients with malignant melanoma have been completed. One obtained three complete responses and one partial responses among 28 evaluable patients (response rate = 14%) at a dose of 250 mg/m^2 as a 24 h continuous infusion.[75] Leukopenia, alopecia and peripheral neuropathy were the chief toxicities. In the other study, 25 patients were treated with a similar regimen and three partial responses were noted (response rate = 12%).[76] In addition, four other patients had marginal responses with a duration of 6–17 months. Neutropenia was the most significant toxicity.[76] When the results of these two studies are combined, the overall response rate for melanoma with this regimen is 13%, with 95% confidence intervals 4.0–22.3%.

A phase II study with a similar regimen obtained no responses amount 18 patients who had renal cell carcinoma.[77]

The use of steroids and antihistamines prior to taxol raises a concern about the possible therapeutic impact of this co-intervention. Steroids are known to be cytotoxic for some cancers[78] and cimetidine has been reported to be associated with remissions of melanoma.[79] Nonetheless, some responses have been observed in patients who received taxol without premedication.[3] A prospective randomized trial would help to determine what impact premedication has upon the response to taxol therapy.

Toxicity

Several toxic effects have been attributed to taxol. Some of these are dose related and others are sporadic. Because the toxic effects are so numerous and potentially serious, taxol should be administered to patients only by physicians who are well acquainted with these effects and who have the facilities and supporting staff required to treat them accordingly.

Myelosuppression

Leukopenia is both frequent and severe among patients treated at the highest doses of taxol. Grade 4 leukopenia (less than 1000 white blood cells or less than 500 total neutrophils) was seen in four of five patients treated with 275 mg/m^2 by 24 h continuous infusion in a phase I trial.[54] Using a 6 h infusion without premedication, one of five patients developed profound neutropenia with subsequent fatal sepsis.[3] Another study[55] using a 6 h infusion produced grade 4 leukopenia in five of 12 patients at 275 mg/m^2 and another study[66] had one grade 4 neutropenia among five courses given at a dose of 265 mg/m^2.

Low doses (less than 100 mg/m^2) tend to produce very little neutropenia[55,66,68] and the area under the plasma disappearance curve of taxol correlates with this toxicity.[52] The observation that patients who had received extensive prior chemotherapy and radiotherapy suffered more severe neutropenia suggested that heavily pretreated patients should be given lower doses of taxol in phase II studies,[66] although this observation was not confirmed by others.[55] The leukopenic effect of taxol is apparently

not cumulative after multiple treatments.[66] Other unidentified factors probably play a role, as this toxicity is unpredictable. A single patient who received four consecutive courses at the same dose had leukopenia grades 4, 0, 2 and 1 in succession.[55]

In phase II clinical trials using 24 h continuous infusions with premedication, leukopenia has been the most significant toxicity. Grade 4 neutropenia was seen in 160 of 281 courses (57%) and two patients died of sepsis in one such study of patients with ovarian cancer.[70] Twenty-eight of 43 patients (65%) developed 'severe or life threatening' leukopenia in another phase II trial for patients with ovarian cancer.[73] In another study of patients with ovarian cancer, nine of 34 patients (26%) required a dose reduction due to severe neutropenia and 20 patients (60%) had transient neutropenia with fever requiring antibiotics.[72] Twenty three of 34 patients had grade 4 neutropenia in another phase II study for patients with malignant melanoma[75] and in 10 of 18 patients with renal cell carcinoma.[77] In summary, at current phase II doses, severe neutropenia is frequent and occasionally life-threatening, but usually is transient and short-lived.

Thrombocytopenia is reported to occur after treatment with taxol, but is less frequent and less severe than the leukopenia. In one phase II study of patients with ovarian cancer, 19% of courses produced grade 1 or 2 thrombocytopenia, while 2% had grade 3 and one patient (0.4%) had grade 4 (platelet count greater than 25 000) thrombocytopenia.[70] Another group reports 9% of patients with platelets less than 50 000 (grade 3–4).[73] Taxol has no apparent effect upon platelet function.[80]

Mild anemia occurred in 20% of patients treated at phase II doses, but the etiology of this finding is unclear.[70]

Hypersensitivity

One of the most dramatic toxicities of taxol is a hypersensitivity reaction. This was reported early in the phase I testing experience.[65,66] The reactions typically occurred a few minutes after beginning an infusion, and were manifest as acute dyspnea, generalized erythema and hypotension. Fatalities during such reactions have been reported.[65]

It is thought that these reactions are probably caused by the release of histamine into the circulation due to the action of Cremophor. This hypothesis is supported by the observation that Cremophor does induce histamine release in dogs.[51] The taxol-related reactions are similar to the syndrome described after the infusion of histamine into humans.[81] and also resemble the anaphylactoid reactions that can follow the infusion of radiocontrast media, which is also known to be histamine mediated.[82] Other Cremophor-based drugs are associated with anaphylactoid reactions.[50]

Given this proposed mechanism, some investigators employed drugs to block both H-1 and H-2 receptors as prophylaxis before taxol.[66] The success of anti-histamines and glucocorticoids in preventing radiocontrast reactions also gave impetus to this approach.[83] A group of phase I investigators has pooled its data on hypersensitivity reactions and these were recently reviewed.[84] Prophylaxis does not confer absolute protection. Close observation of the patient can be safely substituted for prophylactic medications.[3]

One recommended prophylactic regimen administers dexamethasone 20 mg and diphenhydramine 50 mg orally 12 and 6 h before taxol and dexamethasone 20 mg and diphenhydramine 50 mg intravenously just before treatment.[84] It has become common practice to pretreat with cimetidine or ranitidine intravenously just prior to taxol.[70] Physicians who administer taxol must be familiar with early signs of anaphylactoid reactions and have quick access to medications and equipment for emergency resuscitation.[86]

Neuropathy

Peripheral neuropathy is a frequent and sometimes dose-limiting toxicity of taxol. It is predominantly sensory, in a glove-stocking distribution.[54,66] Numbness and paresthesias are the most frequent complaints. Physical signs include diminished proprioception, vibratory sense, pinprick and temperature sensation. Deep tendon reflexes can also be diminished.

This complication is rare at doses less than 200 mg/m^2 and usually begins 1–3 days after treatment.[54,87] Combined therapy with taxol and cisplatin does not appear to worsen the neuropathy.[69] Unlike the ovarian cancer studies where taxol followed cisplatin therapy, two patients had severe exacerbations of neuropathy when they were treated with cisplatin and vinblastine after suffering a relapse of malignant melanoma after taxol.[76]

Nerve conduction studies suggest both axonal degeneration and demyelinating components are present.[87] Sural nerve biopsy of a patient 3 months after a single dose at 225 mg/m^2 showed no microtubule abnormalities and a thinly myelinated

axon suggested possible remyelination.[55] Another patient underwent sural nerve biopsy after her 12th monthly course at 275 mg/m^2. She had severe nerve fiber loss and axonal atrophy with evidence of secondary demyelination. Axonal sprouting was not present and microtubule aggregation was not seen in axons or Schwann cells.[85]

In phase II studies peripheral neuropathy remains a significant concern. In 281 courses at doses from 110 to 250 mg/m^2, 29% of courses were followed by mild paresthesias and in 10% by several paresthesias.[70] In three trials at 250 mg/m^2, mild neuropathy was observed in approximately two-thirds of patients[75,77] and required dose reductions in 10 of 68.[72,75] A phase II study in patients with ovarian cancer treated at 175 mg/m^2 did not report neuropathy as a significant toxicity.[73]

Animal models have provided some insight into possible mechanisms of taxol neuropathy. Repeated injections of taxol into the sciatic nerve of the rat produces loss of Schwann cells and bundles of microtubules in axons.[22–24] These bundles are nearly identical to the bundles described in brain-derived microtubules exposed to taxol *in vitro*,[88] in cultured dorsal root ganglion cells[89] and embryonic chick neurons.[20] Organotypic cultures of mouse spinal cord degenerate after taxol exposure, but treatment with nerve growth factor or stimulation by nerve growth factor enhanced dorsal root ganglion cells after taxol can overcome these toxic effects.[90]

Other neurologic problems have been observed in patients treated with taxol. These include diplopia,[66] seizure which recurred after rechallenge with taxol,[70] proximal muscle weakness,[87] fine motor weakness,[66] headache[3] and adynamic ileus.[54]

Mucositis

At very high doses of taxol given to patients with refractory acute leukemia, the dose-limiting toxicity was oropharyngeal mucositis.[30] At 390 mg/m^2 by continuous infusion given over 24 h, all six courses were complicated by mucositis so severe that patients could not tolerate soft food orally. At 315 mg/m^2, some patients experienced mucositis, but only during their second or third courses, which suggests a possible cumulative effect. The lesion is painful but resolves 5–7 days after treatment. Significant mucositis was seen in less than 5% of patients in phase II testing against ovarian cancer in one study[70] and was not mentioned in abstracted results from three other phase II studies.[72–73,77]

An autopsy series has shown that the lesion involves oropharynx, esophagus and intestines.[36] The findings are most dramatic in the esophagus and are manifest as necrosis associated with mitotic arrest, widely separated chromosomes and dense rings of cytokeratin around the nuclei. Gastric mucosal arrest is seen only in areas of intestinal metaplasia.

Other toxicities

Alopecia is another frequent side effect of taxol and occurred in all patients in a phase II trial of patients with ovarian cancer.[70] The alopecia is complete, involving scalp, eyebrows, eyelashes and pubic hair. This has been reported by several investigators and was apparent in patients treated at doses greater than 150 mg/m^2.[30,65] The hair loss is reversible with time.[65]

A syndrome of arthralgia, myalgias or bone pain has been reported in several series.[30,70,76] This typically occurs 2–3 days after treatment, persists for 2–4 days and does not appear to be related to serositis or rhabdomyolysis.[70] Narcotics[30] or non-steroidal anti-inflammatory drugs[70] have been reported to be useful adjuncts in treating this side effect.

Atrioventricular conduction delay or block was rarely symptomatic but did occur in 29% of patients in a phase II study.[70] One of these patients required a permanent pacemaker. Several other toxicities have been reported infrequently. These include mild nausea and vomiting,[3,66] diarrhea,[67] extravasation cellulitis[55,70] or infusion-site phlebitis,[66] lipid pulmonary embolism,[91] hypertriglyceridemia,[65] and taste perversion.[3]

Conclusion

Taxol is a new drug with a unique mechanism of action and exciting possibilities in the treatment of patients with cancer. Taxol is effective in the treatment of some patients with advanced, drug refractory ovarian cancer, breast cancer and malignant melanoma. Taxol promotes exaggerated stability of microtubules and this probably leads to interference with mitosis as the mechanism of cytotoxicity. Significant clinical toxicity from taxol suggests that it should be used with extreme caution and in a closely supervised setting.

Many basic questions about taxol remain. Further research is required into the roles of microtubules in mitosis and cellular physiology. The develop-

ment of *in vitro* testing to identify patients with sensitive tumors would be beneficial. The mechanisms of drug resistance and ways to overcome these must be explored. Alternation of taxol with microtubule antagonists should be explored further in the laboratory.

Several obstacles remain before taxol enters routine clinical use. Foremost among these problems is that taxol is in short supply and several strategies are currently being employed in attempts to solve this. The unpredictable nature of hypersensitivity reactions with taxol is disturbing and perhaps a superior solvent vehicle will diminish this risk. Growth factors may diminish some of the other toxic effects of taxol, allowing further dose escalation and improved tumor responses. More extensive phase II testing is required to determine what other specific malignancies may respond to taxol therapy. Whether a different schedule of administration is useful and the withholding of premedications should also be considered. Also needed are phase III trials using taxol as a first-line agent in comparison with others in clinical use and to define the role of taxol in combination chemotherapy. Particular attention should be paid to exploration of taxol in non-cross resistant combinations. The introduction of taxol marks a major step in our efforts to care for patients with cancer.

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