Taxol: An Important New Drug in the Management of Epithelial Ovarian Cancer

MAURIE MARKMAN, M.D.

Breast/Gynecology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, and Department of Medicine, Cornell University Medical College, New York, New York

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Taxol, an antineoplastic agent isolated from the Pacific yew, has been demonstrated in three phase 2 clinical trials to have major activity (30 percent overall response rate) in patients with ovarian cancer refractory to cisplatin. The major toxicities associated with the agent are neutropenia (dose-limiting), hypersensitivity reactions, peripheral sensory neuropathy, and cardiac arrhythmias. A recently reported phase 1 trial of the combination of cisplatin and taxol has defined acceptable doses for the two-drug combination to be tested against cisplatin and cyclophosphamide as frontline therapy of advanced ovarian cancer. Taxol has also been examined for intraperitoneal administration in patients with ovarian cancer, with a major pharmacokinetic advantage for peritoneal cavity exposure being demonstrated. Unfortunately, any future development of taxol as an antineoplastic agent in the management of ovarian cancer will be dependent on the finding of an alternative source of the drug, as the current method of obtaining taxol from the bark of the Pacific yew provides insufficient quantities for large-scale clinical use.

INTRODUCTION

Epithelial ovarian cancer is one of the most responsive solid tumors to cytotoxic chemotherapeutic agents, with approximately 80 percent of patients experiencing objective responses to cisplatin-based combination regimens [1-5]. In addition, approximately 40-50 percent of all patients with advanced ovarian cancer will be found to have no clinical evidence of disease (by physical examination, CT scan) at the completion of five to six months of therapy. Unfortunately, despite the high response rate observed, the majority of women with advanced (stage III/IV) disease will ultimately suffer a recurrence and die of complications of their malignancy. Thus, there is a critical need to find new active antineoplastic agents in the treatment of ovarian cancer.

Taxol, a natural product obtained from the bark of the Pacific yew, Taxus brevifolia, has been demonstrated in several clinical trials to possess a remarkable degree of activity in patients with ovarian cancer resistant to cisplatin [6-8]. In this review, the basic biology supporting the use of taxol as an antineoplastic agent will be presented briefly, followed by a discussion of the clinical data currently available on the pharmacology and toxicity of the drug, as well as its efficacy in patients with advanced ovarian cancer.

Abbreviation: GOG: Gynecologic Oncology Group

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EXPERIMENTAL EVALUATION OF THE ACTIVITY AND TOXICITY OF TAXOL

While a crude extract of the Pacific yew plant was originally demonstrated to possess antineoplastic activity, it was not until the 1970s, when taxol was identified as the active cytotoxic ingredient of the preparation, that significant interest developed in the agent [9]. Taxol has been demonstrated in a number of experimental systems, both in vitro and in vivo, to possess a wide spectrum of antineoplastic activity [10,11]. Impressive tumor cell kill is observed in non-human hemalogic as well as solid tumors. In addition, the drug has been shown to be cytotoxic to a number of human tumors implanted into nude mice, including ovarian cancer [12,13].

There has been intense recent interest in the mechanism of taxol cytotoxicity. The drug produces a number of effects on neoplastic and normal cells, but its major mechanism of action appears to be due to its ability to cause stabilization of microtubules [10]. Microtubules are important in cell division and in several vital cellular functions, including maintenance of cell shape, motility, and intracellular transport. Presumably, taxol-induced interference with the microtubule system leads to disruption of one or more of these important cellular activities and subsequent cell death.

Of considerable interest are two distinct patterns of microtubule bundling which have been observed in a small group of patients with acute leukemia treated with taxol [14]. In patients responding to taxol, the bundling, visualized by indirect immunofluorescence, persisted in the cells even in the absence of taxol, while in the resistant patients the microtubular dysfunction was reversible [14]. This observation supports the importance of stabilization of microtubules as the major mechanism of taxol-induced cytotoxicity and also suggests that cells able to reverse or prevent the defect will be resistant to the agent. Finally, if the experience with the indirect immunofluorescence assay for taxol activity in acute leukemia can be confirmed to be of value in other tumors, particularly ovarian cancer, this procedure would be a useful in vitro test to predict the clinical utility of the drug in individual patients. In addition to its antitumor activity, pre-clinical evaluation of taxol has shown it to be toxic to the gastrointestinal tract, bone marrow, and lymphocytes [10]. These findings were not surprising, as the affected tissues are composed of rapidly dividing cells, which are most susceptible to the commonly used antineoplastic drugs. Taxol was, however, also associated with unique side effects not observed with other agents. As the drug is poorly soluble in water, it was necessary to formulate the drug in cremophor (polyoxyethylated castor oil) [15]. In dogs, this vehicle can produce profound reactions, including vasodilation, hypotension, and death, presumably secondary to a hypersensitivity reaction [10,15]. Thus, it is not surprising, as will be discussed later, that the clinical administration of taxol in cremophor can be associated with severe hypersensitivity reactions [16].

PHASE 1 CLINICAL TRIALS OF INTRAVENOUS TAXOL

Taxol has been administered by a variety of schedules in almost a dozen phase 1 clinical trials [17–25]. Therapy has ranged from as rapid an intravenous infusion as a single dose delivered over several hours, to as slow an infusion as the same dose administered over 24 hours [17–25]. While the incidence of hypersensitivity reactions appears to be greatest in the series employing rapid infusions, and lowest with the
24-hour infusions, it is not possible to be certain that the improvement in the toxicity profile is secondary to the change in the rate of infusion or simply to the recognition of the potential for this toxicity and the institution of measures to prevent the event (prophylactic treatment with corticosteroids, H-1 and H-2 histamine antagonists) [16].

The dose-limiting toxicity of taxol has been shown to be the development of neutropenia [10,17–25]. Most patients experience at least moderate neutropenia following taxol administration. Severe thrombocytopenia has been uncommon with the use of this agent. Additional, less common toxicities observed with the administration of taxol include: mucositis (which may only develop with late courses, suggesting a cumulative dose effect), dysphagia, diarrhea, emesis (usually mild in severity), alopecia (which may be sudden in onset and can involve all areas of the body), neurotoxicity, cardiac arrhythmias, and hypersensitivity reactions.

The most common taxol-associated neurotoxicity is a peripheral sensory neuropathy, although motor dysfunction has been described [10]. The incidence of neurotoxicity appears to be greatest in patients receiving doses of taxol > 170 mg/m². There is no clear relationship between prior cisplatin administration and the development of a taxol-associated peripheral neuropathy. With very high-dose taxol administration (> 300 mg/m²), transient myalgias and arthralgias have been described, and at least one patient has experienced a seizure following taxol administration.

Asymptomatic bradycardia is very common following taxol administration, but this transient event does not appear to predict more serious cardiac toxicity [10]. Of greater concern is the fact that atrioventricular block and ventricular arrhythmias, including ventricular tachycardia, have been observed following infusions of taxol. While chest pain has also been noted in patients receiving the agent, it is not clear if such pain is of cardiac origin or is rather one form of a hypersensitivity reaction to the taxol or its vehicle [16].

As previously noted, hypersensitivity reactions to taxol were common in the early phase 1 clinical trials [16]. In fact, in the Memorial Sloan-Kettering Cancer Center trial, this effect of the preparation was felt to be the dose-limiting toxicity of the agent [24]. The pattern of the clinical reactions observed is classic for a type I hypersensitivity reaction (urticaria, dyspnea, bronchospasm, hypotension). Patients can experience some or all of the symptoms of hypersensitivity within minutes of their first exposure to taxol [16]. Thus, it is more likely that the mechanism of hypersensitivity is a direct effect of the preparation itself (taxol or cremophor), causing the release of histamine, rather than an indirect effect mediated through IgE antibodies. Fortunately, the incidence and severity of allergic reactions appears to be reduced by pre-treating patients with corticosteroids and histamine blockers [16]. The specific pre-treatment protocol recommended by the National Cancer Institute for patients receiving taxol includes: dexamethasone, 20 mg administered orally or intravenously 14 and seven hours prior to taxol delivery; diphenhydramine, 50 mg administered intravenously 30 minutes prior to taxol; and cimetidine or ranitidine, 300 mg or 50 mg, respectively, administered intravenously 30 minutes prior to taxol.

The maximally tolerated dose of taxol in phase 1 clinical trials was found to be highly dependent on the extent of pre-treatment prior to taxol administration. In patients with limited cytotoxic drug exposure, it was possible to deliver 200–225
mg/m² of taxol with acceptable marrow toxicity. In contrast, patients with extensive prior chemotherapy were only able to tolerate 110–170 mg/m² of the agent.

The peak plasma concentrations of taxol in patients following intravenous administration have been found to range between 2.3–8.1 micromolar with doses of 175–390 mg/m² [10]. Of interest is the fact that the concentrations observed in the plasma with intravenous delivery have been shown to be cytotoxic against human tumor in vitro [22]. Although taxol is extensively protein-bound, it is rapidly cleared from the plasma. Less than 10 percent of the agent is found in the urine, and the available data suggest that metabolism, biliary excretion, or tissue binding are responsible for the removal of the drug from the circulation.

In the several phase 1 and limited non-ovarian phase 2 trials, antineoplastic activity has been observed for taxol in melanoma, leukemia, and non-small cell lung, gastric, colon, breast, and head and neck cancers [10,26,27]. Phase 2 trials are currently in progress for a number of tumor types. In addition, phase 1 trials of taxol with the colony stimulating factors G-CSF and GM-CSF, and a combination regimen of taxol with cisplatin, are nearing completion [28].

DEFINITION OF REFRACTORY OVARIAN CANCER

Before turning our attention to a discussion of the activity of taxol in refractory ovarian cancer, it is important that criteria for patient inclusion in this clinical grouping be carefully defined. It has been common in the oncology literature to lump together into the category of “refractory ovarian cancer” all patients who have previously received cisplatin (or carboplatin) and who have persistent or recurrent disease. Thus, papers discussing the results of new drugs or drug combinations in patients with this clinical entity have reported the activity of the agent(s) in a very heterogeneous group of individuals.

It is now known that patients who have previously responded to cisplatin or carboplatin and who have developed recurrent disease may respond a second time to the agents [29–31]. Several studies have documented that the secondary response rate is significantly influenced by the duration of the treatment-free interval between the last dose of the frontline platinum treatment and the first dose of the secondary platinum therapy. For example, in a recent retrospective review of secondary cisplatin therapy in patients with ovarian cancer at the Memorial Sloan-Kettering Cancer Center, 25–35 percent of patients with a treatment-free interval of five to 24 months following the completion of the frontline therapy responded to a second course of cisplatin, while > 75 percent of patients with a treatment-free interval of more than two years responded [29]. Thus, it is inappropriate to consider a patient with recurrent ovarian cancer to have “refractory” disease, especially if the individual has previously responded to cisplatin and the treatment-free interval is at least six months.

In contrast, patients who have recently received cisplatin and who have persistent bulky disease (no or minor response to therapy or actual disease progression) are a far more difficult group to treat. Numerous studies have documented the failure of second-line therapy in this clinical setting to have a significant effect in terms of either response rate or survival [1,32,33]. It is this patient population which should appropriately be classified as having refractory ovarian cancer. The discovery of an agent with significant antineoplastic activity in this disease setting would be an important clinical finding.
INTRAVENOUS TAXOL IN REFRACTORY OVARIAN CANCER

With this background, we now turn to the clinical trials of taxol in patients with ovarian cancer. In the early phase 1 trials of the agent, antineoplastic activity was observed in several heavily pre-treated individuals with ovarian cancer [10,17,23]. This finding led to the conduct of several phase 2 trials of taxol in patients with ovarian cancer who had previously been treated with cisplatin-based therapy.

Investigators at the Johns Hopkins Oncology Center recently reported the results of a trial of taxol administered as a 24-hour infusion to patients with advanced ovarian cancer [6]. Doses administered in this trial ranged from 110 to 250 mg/m². Treatment was repeated every 22 days, assuming acceptable toxicity and lack of disease progression. Twelve of 40 (30 percent) evaluable patients responded, with response durations of three to 15 months. The mean number of chemotherapy regimens administered to this group of patients prior to the administration of taxol was 2.7, with the 12 responding patients having received a mean of 3.0 previous regimens. Thus, this group was a heavily pre-treated patient population. Seven additional patients had more minor responses (not meeting the criteria for a partial response), which included clinically relevant improvement in cancer-related symptoms.

The toxicity observed in this trial was similar to that reported in the phase 1 studies. Fifty-seven percent of courses were associated with grade 4 (National Cancer Institute Common Toxicity Scale) leukopenia, the dose-limiting toxicity. Grade 4 thrombocytopenia was only noted following a single course. While peripheral neurotoxicity was common, it was not severe in any patient.

In a preliminary report, the Gynecologic Oncology Group (GOG) has observed results similar to the Johns Hopkins trial [7]. Patients were treated with taxol at a dose of 175 mg/m², administered as a 24-hour infusion. Treatment was delivered every three weeks, assuming recovery from previous toxic effects of the agent. Among 27 evaluable patients in this study who had either failed cisplatin therapy or who had progressed within six months of completing their frontline chemotherapy program, eight responses (30 percent) were observed, including two clinically defined complete and six partial responses. Seven responses (50 percent) were noted among the 14 evaluable patients with recurrent disease (treatment-free interval greater than six months). Dose-limiting toxicity was again found to be leukopenia (65 percent of courses associated with white blood cell count < 2,000/mm³). Severe thrombocytopenia (platelet count < 50,000/mm³) was observed following 9 percent of courses.

Finally, investigators at the Albert Einstein Cancer Center (in New York) and the Montefiore Medical Center have reported the preliminary results of a phase 2 trial of taxol, administered at a dose of 250 mg/m², as a continuous infusion over 24 hours to 34 patients with advanced measurable ovarian cancer [8]. Thirty of the 34 patients had previously received cytotoxic chemotherapy. Of the 29 patients evaluable for response, six (21 percent) achieved either a complete (one patient) or partial (five patients) response. Twenty patients (59 percent) experienced neutropenic fevers, while six patients (18 percent) developed significant peripheral neuropathies, which required a reduction in dose.

In summary, these three clinical trials have firmly established major activity for taxol in patients with ovarian cancer refractory to cisplatin-based therapy. As a result of the antineoplastic activity demonstrated in patients in the refractory disease setting, the GOG has initiated a randomized trial of taxol plus cisplatin compared to...
cyclophosphamide plus cisplatin as initial therapy for patients with advanced bulky ovarian cancer. While the results of this trial will not be available for several years, it is hoped that the addition of an agent active in cisplatin-resistant disease to the frontline program will increase the overall response rate to therapy, the duration of responses, and, ultimately, the survival of individuals with advanced ovarian cancer.

PHASE 1 TRIAL OF INTRAPERITONEAL TAXOL

Over the past decade, investigators at a number of institutions have explored the potential for the intraperitoneal administration of cytotoxic and biological agents as treatment for patients with ovarian cancer [34]. The rationale, pharmacology, unique toxicities, and efficacy of this approach, using a variety of antineoplastic agents, has been presented in detail elsewhere and will not be discussed here [34]. With the demonstrated activity of taxol in patients with advanced ovarian cancer, however, it was natural that the drug should be examined for its safety, pharmacology, and potential efficacy when delivered by the intraperitoneal route.

The rationale supporting the intraperitoneal use of taxol is strengthened by limited experimental data suggesting that the cytotoxicity of the agent against leukemia cells is related to both the duration of exposure and the concentration of drug in contact with the malignant cells [14]. With higher drug concentrations and longer exposure times, there is an increased cytotoxic effect of the agent [14]. Unfortunately, these experiments have not been performed with solid tumors. Thus, it is not possible to know for certain if the observations made with leukemic cell lines are applicable to ovarian cancer cell lines or, most important, to human ovarian cancer.

In a preliminary analysis of an ongoing phase 1 intraperitoneal taxol trial being conducted at the Memorial Sloan-Kettering Cancer Center, it has been demonstrated that the agent can safely be administered into the peritoneal cavity with a major pharmacokinetic advantage for cavity exposure compared to that of the systemic compartment [35]. The drug does, however, leave the cavity in significant concentrations, as grade 3–4 (National Cancer Institute Common Toxicity Scale) bone marrow suppression has been observed at the highest dose levels tested. The maximally tolerated intraperitoneal dose of taxol has not as yet been defined, and it remains uncertain if the limiting toxicity will be secondary to a local or systemic effect of the agent.

CONCLUSION

Taxol has been demonstrated to be a highly active drug in patients with advanced ovarian cancer. Unfortunately, at the present time, further exploration of the potential utility of this drug in patients with ovarian cancer, or other malignancies, is hampered by severe limitations on the supply of the agent. The drug is currently obtained from the bark of the Pacific yew tree. This method of obtaining taxol requires that the tree be killed, and the resource is not easily renewed. Taxol has a complicated structure, and, to date, research has not been able to synthesize the agent. Thus, efforts have focused on finding an alternative source of the drug from other trees of the Taxus species [36,37] or from cell culture [38]. For example, if the active drug could be extracted from the needles of the tree, rather than the bark, it would be possible to obtain the agent without sacrificing the tree. It can reasonably be hoped that such a source will be found, and that this important agent will
ultimately become available for general use in patients with ovarian cancer and other malignancies.

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