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Outpatient Administration of Paclitaxel

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Introduction

Paclitaxel (Taxol®, Bristol-Meyers Squibb), antineoplastic agent made from the bark of the Pacific yew tree, is undoubtedly one of the most exciting agents to be evaluated over the past decade. Paclitaxel has demonstrated significant promise against ovarian and metastatic breast cancer, and appears to be the most effective single agent to date for non-small-cell lung cancer in trials conducted by Eastern Cooperative Oncology Group (ECOG).

The toxicities of paclitaxel include myelosuppression, neuropathy, cardiac arrhythmias, and hypersensitivity reactions. Based on initial observations suggesting that the incidence of hypersensitivity reactions may be higher with the shorter infusion durations, later trials were developed using 24-hour infusions and prophylactic antiallergic regimens. Using this method of administration, which generally requires an inpatient hospital admission, the incidence of hypersensitivity reactions was approximately 3%.

In this article, we will examine the results of ongoing trials using a shorter three-hour infusion time of paclitaxel given at various doses and focus on the issues of dosing and safety, efficacy, and method of administration thus alleviating the need for inpatient hospital admission and thereby maximizing the cost effectiveness of this drug therapy.

Dosing and Safety

Severe hypersensitivity reactions were identified early in the course of phase I clinical trials of paclitaxel; the majority occurred in association with a short infusion time of paclitaxel (one to three hours). As a result of these observations, the length of administration was increased and a premedication regimen that included steroids and h1 and h2 histamine-receptor blockers was introduced. Subsequent studies proved that these results were safe.

Recent review of the published phase I trials of paclitaxel suggests that the administration of premedications may play a more important role in reducing the occurrence of severe hypersensitivity reaction than the dosing schedule itself. This observation is supported by a large randomized trial which compared two doses of paclitaxel (175 and 135 mg/m^2) and two schedules (24 and three hours) using a bifactorial design. The incidence of severe hypersensitivity reactions was 1.2% with the longer infusion and 2.2% with the shorter one. Of note, there also was no apparent effect of dose on the occurrence of severe hypersensitivity reactions in this trial (1.4% with the higher dose, 1.9% with the lower).

Paclitaxel has demonstrated significant promise against ovarian and metastatic breast cancer, and appears to be the most effective single agent to date for non-small-cell lung cancer.

A recent study by Schiller et al demonstrated that higher paclitaxel doses up to 300 mg/m^2 can be administered over three hours with the standard premedications. One of 35 patients (2.8%) had a grade 3 anaphylactic reaction within one minute of initiation of his second dose of 250 mg/m^2 of paclitaxel requiring treatment with diphenhydramine, fluids, and oxygen. Rechallenge was not conducted. Another patient developed facial flushing and severe headaches approximately 15 minutes following completion of his first cycle of 300 mg/m^2 of paclitaxel. No treatment was given, and the patient received subsequent courses of paclitaxel at the same dose without any recurrence of the symptoms. The author concluded that with proper monitoring and pre-medication, high doses of paclitaxel can be safely administered in the outpatient setting.

More studies are currently being conducted to evaluate one-hour infusion of paclitaxel in combination with other antineoplastic agents, and the preliminary reports were published in the proceedings of the 1994 Annual Meeting of the American Society of Clinical Oncology.

The effects of paclitaxel on the bone marrow, however, are dose related. Interestingly, the previously mentioned bifactorial randomized trial demonstrated striking decreases in bone marrow suppression associated with the three-hour paclitaxel infusion. The short infusion was associated with a 17% incidence of grade 4 granulocytopenia and no febrile neutropenia, whereas 74% of the patients given paclitaxel over 24 hours developed grade 4 granulocytopenia and 12% febrile neutropenia. Pharmacokinetic data indicated both area-under the curve (AUC) and Cmax values to be substantially higher when identical doses of paclitaxel are administered over three hours as compared to 24 hours. However, the percentage decreases in both the white blood cell counts and the absolute neutrophil counts follows an Emax model that relates these parameters to the dura-

tion that the plasma concentration of paclitaxel is maintained about 0.1 umol/L.

Drug sequencing also plays a significant role in toxicities when 24-hour infusion of paclitaxel is combined with cisplatin or doxorubicin. Increased neutropenia and decreased paclitaxel clearance are observed when cisplatin is administered before paclitaxel regardless of dose. The potential mechanism is the inhibition of cytochrome P-450 dependent paclitaxel metabolizing enzyme by cisplatin. Cumulative thrombo-cytopenia, infections, and severe mucositis become the dose limiting toxicities when paclitaxel 125 mg/m^2 24-hour infusion precedes doxorubicin 48 mg/m^2 48-hour infusion; when the sequence is reversed, the doses of both agents can be escalated. Doxorubicin level was also noted to increase by 30% when paclitaxel was administered prior to doxorubicin.

Many combination regiments using one-hour and three-hour paclitaxel infusion in various diseases are currently undergoing evaluation and were reported at the 1994 Annual Meeting of the American Society of Clinical Oncology. The effect of drug sequencing was not studied in these preliminary reports, but it is speculated that this effect in the three-hour infusion is probably less significant due to the overlapping kinetic factors.

Peripheral sensory neuropathy can also occur with paclitaxel and is dose related but not scheduled related. Arthralgias and myalgias sometimes occur in association with peripheral neuropathy. Schiller's report suggested that troublesome arthralgias and myalgias are more prominent with high doses (>250 mg/m^2) administered over three hours in comparison with similar doses over 24 hours and lower doses (210 mg/m^2) over three hours. In this study, 27 of 111 courses (24%) required narcotics for pain control. Prednisone also appeared to promptly alleviate the symptoms of many of these patients.

Other side effects, such as nausea/vomiting, mucositis, and diarrhea seen with paclitaxel administration are more associated with dosing than with schedule effects.

Efficacy

The key question surrounding both the dose and the schedule issues of paclitaxel is the effect on antitumor efficacy. At the present time, efficacy data comparing different infusion durations are available from only one clinical trial. National Cancer Institute of Canada (NCIC)/European investigators randomized patients with platinum-pre-treated ovarian cancer in a 2x2 factorial design to one of two doses of paclitaxel, 135 and 175 mg/m^2, and one of two infusion durations, three or 24 hours. Neither response rates (17% vs 20%) nor survival rates differed for patients on the three- and 24-hour arms. However, the 24-hour schedule was associated with substantially more grade 4 neutropenia (74% vs 17%) and a higher incidence of febrile neutropenia (12% vs 0%). Thus, only 76.5% of patients in the 24-hour group received at least 90% of the planned dose as compared with 92% in the three-hour arm.

One question which needs to be addressed is whether the support of granulocyte colony-stimulating factor (G-CSF) will allow maintenance of chemotherapy dose-intensity of the 24-hour arm. The Gynecology Oncology Group (COG) is currently conducting a randomized phase III trial in ovarian cancer addressing the role of G-CSF with a 24-hour infusion of high dose paclitaxel (250 mg/m^2) with the

Table 1.
Manifestations and Recommended Management of Hypersensitivity Reaction Associated with Paclitaxel Infusion

Major manifestations:	• Respiratory distress + bronchospasm, hypotension, angioedema
Other manifestations:	• Flushing, urticaria, rashes, chest and extremity pains
Recommended premedications:	• Dexamethasone 20 mg IV or PO at -12 and -6 hour • Diphenhydramine 50 mg IV at -30 min • Cimetidine 300 mg or ranitidine 50 mg IV at -30 min
Recommended precautions:	• Medical personnel should be available (especially for the first two treatments) • Emergency equipment, fluids, pressors, and other injectable drugs (e.g., epinephrine, diphenhydramine, steroids) close to bedside
Recommended treatment:	*Major manifestations:* • discontinue paclitaxel immediately • diphenhydramine 25-50 mg IV as indicated • pressors, fluids, epinephrine as indicated • dexamethasone 20 mg IV every 6 hours for persistent symptoms *Minor manifestations:* • diphenhydramine 50 mg IV every 4 to 6 hours as indicated • symptomatic treatment
Recommended rechallenge:	• Dexamethasone 20 mg IV every 6 hours for 4 doses (may begin as soon as patient is stabilized); the last dose should be given 30 mins before the rechallenge • Diphenhydramine 50 mg IV and cimetidine 300 mg or ranitidine 50 mg IV 30 mins before the rechallenge • A freshly prepared solution of paclitaxel should be given at 10% of the rate required to deliver the solution over 24 hrs; this rate should be maintained for 2 hours. If no major reaction occurs, the rate should be increased gradually over the next 6 hours to the original 24-hour rate. If the original HSR occurred after a negligible dose of paclitaxel, the full does should be readministered. If a substantial fraction of the dose was infused before the HSR, the rechallenge dose should be the remaining dose fraction. Medical personnel should be available.

Table 2.
Commercially Available Administration Sets for Delivery of Paclitaxel

I. Institutional Administration

Catalog Number	Description	Type of Pump
ABBOTT (1-800-222-6883)		
11140-48	Proximal set (container to pump) +	Omni-Flow 4000 series
1736-48	Distal extension set (pump to patient)	
2427-02	Vented dual channel set	Lifecare 5000 plus
1772-01	Vented set	Lifecare Macro (flow rate 999ml/hr)
9252-68	Vented set	Lifecare Macro (flow rate 99.9ml/hr)
BAXTER (1-800-933-0303)		
2C1042	Vented Set	Flo-Guard 8000 series
1C8355S	Vented with in-line filter	Flo-Guard 6000 series
IMED (1-800-854-2033)		
2260	Vented Set	Gemini PC 1 & 2
2262	Non-vented set	Gemini PC 1 & 2
2264	Vented set with in-line filter	Gemini PC 1 & 2
9630	Vented set	IMED 900 model
9635	Non-vented set	IMED 900 model
IVAC (1-800-854-7128)		
59953 C20350	Vented & non-vented set + extension set 14" with in-line filter	IVAC 590 & 599 model
MCGAW (1-800-854-6851)		
V8333	Vented & non-vented set	AccuPro pump

II. Ambulatory Infusion Pump

ABBOTT	
Pancretec Provider 5000 Pump	McGaw Excel 250, 500, or 1000 ml polyolefin container + Abbott/McGaw adaptor (#11075) + Abbott Lifeshield Anesthesia Pump set-OL polyethylene-lined cartridge-tubing set (#13503) + IVEX-HP in-line filter (#4524)
BLOCK (1-800-944-1501)	
Verifuse Ambulatory Infusion Pump	McGaw Excel polyolefin container + Block vented (V021011) or non-vented set (V021014) with 0.22 micron filter or Reservoir set (V021012) = Non-PVC 120 ml container + tubing set
PHARMACIA DELTAC (1-800-426-2448)	
CADD-1, CADD-PLUS, CADD-PCA	McGaw Excel polyolefin container + TOTM remote reservoir adaptor cassette (#21-7016) [bag spike and 60-inch tubing included]**

III. Filters for Administration of Paclitaxel

Catalog Number	Description	Type of Pump
Abbott 4524-58	IVEX-HP	various
Abbott 4521-48	IVEX-HP	various
Abbott 2679-48	IVEX-2	various

**in-line filter not included in the current product, may add filter at the end of tubing but non-luer-lock system needs to be taken into consideration if patient is to receive treatment at home

secondary goal to evaluate the dose of the cytokine required. Other trials in patients with breast and lung cancer are ongoing to address the efficacy of higher doses of paclitaxel with or without G-CSF and determine the impact of different administration schedules on therapeutic outcomes. Although in-vitro data indicated that one-third activity was recorded with three-hour exposure time vs. 24-hour exposure time, in previously treated ovarian and breast cancer patients, the endpoint of the treatment is primarily palliative which makes the toxicities of the therapy, cost of treatment and the quality of life of the patients far outweigh the potential differences in the response rate.

Method of Administration

Because of the unique nature of paclitaxel, with its complicated formulation and potentially significant side effects, special preparation of the paclitaxel infusion and monitoring of patients are required.

Hypersensitivity reactions, particularly anaphylactoid signs and symptoms, are a major concern during paclitaxel administration. The majority of the hypersensitivity reactions are reported to occur within 5-10 minutes of the initiation of infusion and during the first and second doses of paclitaxel. The manifestations and recommended management are listed in Table 1. For outpatient administration of paclitaxel over three hours, a test dose or close monitoring with recommended premedications is being used.

Prior to the availability of Dr. Schiller's report, three patients at our institution (11 courses) were treated with high dose paclitaxel (250 mg/m^2) infused over six hours in the outpatient infusion center. All patients were pre-treated with standard antiallergic medications and did not receive a test dose. All three patients tolerated their therapy without any complications.

Another consideration is the interaction of the drug with the administration device. Paclitaxel is poorly soluble and requires a vehicle containing polyoxyethylated castor oil (Cremophor EL) which is known to leach phthalate plasticizers (e.g., diethlhexylphthalate [DEHP]) from polyvinylchloride (PVC) bags and administration sets. Glass or

polyolefin containers are recommended for preparation of the solution. Non-PVC (e.g., polyethylene-lined) tubing sets with an in-line 0.2 micron filter are also recommended by the National Cancer Institute. Table 2 lists the current commercially available administration sets for delivery of paclitaxel in an institutional setting or via ambulatory infusion pump.

Current stability data indicates that the drug remains chemically and physically stable for 48 hours at 0.3 - 1.2 mg/ml at room temperature and normal fluorescent light. For a three-hour infusion, most of the solution can be diluted in 300 - 500 ml 0.9% sodium chloride or 5% dextrose. Compatibility information of paclitaxel solutions with other medications is minimal. A recent study was published by Trissel and Martinez on turbidimetric assessment of the compatibility of Taxol® with 42 other drugs during a simulated Y-site injection. The combination of paclitaxel with four drugs, including chlorpromazine, hydroxyzine, methylprednisolone and mitoxantrone, resulted in decreases in the inherent surfacant haze from the Taxol® formulation. This loss may indicate an interaction between the drugs and the formulation. Combination with amphotericin B resulted in an increase in turbidity which eventually under went separation and layering. Chemical stability of the drug combinations mentioned above were not conducted in this study.

Local venous effects can also occur with administration of paclitaxel. Tenderness, darkening and hardness can sometimes be noted several inches above an intravenous site through which the drug has been infused. These effects tend to be delayed, sometimes becoming apparent one to three weeks after treatment, and can last indefinitely. Clinical data with paclitaxel extravasation appears to cause minimal long-term effects, although patients can experience pain, edema, and erythema at the site followed by a brawny (rough) appearance of the skin.

In a recent report where paclitaxel 250 mg/m^2 was infused through peripheral intravenous access over 24 hours, three out of 24 patients developed grade 2 severity skin reactions based on the Common Toxicity Criteria developed by the NCI. In one patient, histopathologic evidence of marked soft-tissue necrosis was documented. This report suggested that paclitaxel is a vesicant and that the severity of the soft-tissue injury should be classified as moderate. Additionally, this drug also appears to cause delayed soft-tissue reactions such as those that have been observed with vinblastine. All patients receiving paclitaxel should be monitored for extravasation.

Treatment options for paclitaxel extravasation are not well documented, and the role of hyaluronidase is unknown. A protocol presently used by The Johns Hopkins Oncology Center recommends close observation and minimization of the amount of drug extravasated by aspiration before removing the intravenous catheter. Following removal of the catheter, warm compresses are applied to the extravasation site for 24 hours. Intradermal infiltration of the site with normal saline to dilute paclitaxel in the tissue does not appear to increase effectiveness. There is no data available to indicate any difference in the incidence of extravasation between the three-hour and the 24-hour infusions.

Conclusion

Current data indicates that a three-hour infusion of high-dose paclitaxel is safe, well-tolerated and does not result in a higher incidence of hypersensitivity reactions than the 24-hour infusion. No unexpected side effects or toxicities were observed, with the possible exception of arthralgias and myalgias. If proper premedications and monitoring are provided, paclitaxel can be safely administered via a shorter infusion time in an outpatient setting, resulting in considerable cost savings and improvement in convenience for patients.

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Editor's Note: *References are available upon request.*