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A phase I study of ambulatory continuous infusion paclitaxel

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Chemotherapy given by continuous infusion may have different toxicity profiles and efficacy than when given by bolus administration. Thirty-one patients with refractory tumors entered a phase I trial in which paclitaxel was administered for 7 days by continuous infusion every 28 days. Only one patient required hospitalization for treatment, because of an initial poor performance status, and most carried out normal activities on an ambulatory basis. After the first three patients, patients were entered in cohorts of five with the starting dose of 120 mg/m^2. Each subsequent cohort was begun at a dose 10% higher than the previous cohort. Later courses within each cohort were increased 10% in an individual patient, if toxicity allowed. Nausea was rare. Of 15 patients with a soft tissue sarcoma refractory to doxorubicin, dacarbazine, ifosfamide, and etoposide, there were: one partial response (PR), five stable diseases and eight progressive; one patient was not evaluable for response. The PR occurred in a patient with a very aggressive sarcoma and very bulky disease, and was maintained for more than 1 year. We conclude that paclitaxel given by ambulatory continuous i.v. infusion is well tolerated with a maximally tolerated starting dose of 160 mg/m^2.

Key words: Chemotherapy, continuous infusion, paclitaxel, sarcoma, taxol.

Introduction

Paclitaxel (Taxol) is the first member of the taxane class of drugs to enter clinical trials and receive FDA approval. This natural product, produced from the pacific yew, was identified more than 20 years ago, but severe hypersensitivity problems in early phase I trials slowed its development as a feasible drug.[1] Subsequently, premedication with anti-histamines, combined with slower administration of the drug itself, made paclitaxel a viable therapeutic agent. Paclitaxel has demonstrated activity in several tumor types including ovarian cancer, breast cancer, non-small cell lung cancer, small cell lung cancer, and head and neck cancer.[2–6] The most important mechanism of action of paclitaxel is felt to be the stabilization of tubulin polymerization, although other mechanisms may also play a role.[2–4] Microtubules are formed from polymers of tubulin subunits and have a number of cellular functions, most prominent being the formation of mitotic spindles.[3] Paclitaxel stabilizes microtubules by inhibiting the dissociation rate of tubulin subunits from the polymerized tubules.

Although paclitaxel is highly protein bound (about 95–98%),[2–4] its plasma half-life is about 1.5–6 h. The major mechanism of systemic clearance is not well defined. Renal elimination is not felt to be a major mechanism of drug clearance, while hepatic elimination is more important, and dose modification based on hepatic function has been suggested.[2–4,7] Phase I trials have demonstrated large volumes of distribution (55–183 l/m^2), likely due to binding to an intracellular compartment such as tubulin.[3]

There has been increasing interest in the administration of cancer chemotherapy by continuous infusion, since continuous infusion chemotherapy results in exposure of the tumor to cytotoxic drugs for a more prolonged period of time than does bolus intermittent administration. Thus, continuous infusion chemotherapy may be more efficacious than bolus chemotherapy for tumors with low growth fractions, as is felt to occur in many solid tumors.

Paclitaxel is a logical drug to study as an infusional agent for two reasons. First, on a theoretical basis one would expect a longer exposure of low growth fraction tumors to drug to be more efficacious. *In vitro* studies suggest that longer exposure to paclitaxel results in a greater tumor cell kill. Second, the infusion

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of paclitaxel over relatively short periods of time has been associated with significant toxicity. Some of this toxicity may be due to the cremophor, the vehicle in which Taxol is dissolved. The acute toxicity of a number of other drugs is decreased by continuous infusion as compared to bolus therapy. For example, the cardiotoxicity of doxorubicin, the acute nausea and vomiting of DTIC (reviewed in Skibitz[8]), and the systemic toxicity of amphotericin B (another drug in which detergent solubilization is necessary).

Micromolar concentrations of paclitaxel arrest cells in mitosis and have been shown to result in the formation of microtubule bundles and asters.[2,3] However, paclitaxel is often cytotoxic or cytostatic at much lower concentrations (about 1–20 nM), and recent studies suggest that such low concentrations can inhibit the progression of cells from mitosis to the G_1 phase[9,10] and result in apoptosis.[9] Interestingly, this ability to inhibit progression from M to G_1 was only present during the time of microtubule formation; this effect was lost after spindle formation occurred.[10] Also of interest is the fact that paclitaxel accumulated in HeLa cells during incubation at 10 nM for 20 h and much of the accumulated drug remained intracellular after washing, suggesting it was bound to intracellular molecules, likely microtubules.[9] In addition, a variety of *in vitro* studies have found that an increase in exposure time to drug resulted in an increase in cytotoxic activity.[4] Taken together, these data provide rationale for administration of paclitaxel at a relatively low dosage rate for a prolonged period of time.

The potential therapeutic benefits of prolonged continuous infusion chemotherapy led us to perform a phase I study of a continuous infusion of paclitaxel. This study had three objectives: (i) to determine the toxicity profile and the maximum tolerated dose (MTD) of a 7 day continuous infusion of paclitaxel, (ii) to evaluate the feasibility of administering this treatment on an ambulatory basis, and (iii) to estimate the response rate of soft tissue sarcomas refractory to doxorubicin, DTIC, ifosfamide and etoposide to this regimen.

Materials and methods

Thirty-two patients at the University of Minnesota entered this study between November 1993 and April 1996, 29 starting with a 7 day infusion. All patients had biopsy proven locally advanced or metastatic soft tissue sarcomas, or other refractory solid tumors; 10 of 15 sarcomas were high grade. All patients had a Karnofsky performance status of 40% or above. All patients met the following criteria: (i) estimated life expectancy of greater than or equal to 2 months, (ii) age 18 years of age and older, (iii) leukocyte count greater than or equal to 3500 ml (granulocytes greater than or equal to 1 500 ml), (iv) platelet count greater than or equal to 100 000 ml, (v) creatinine less than or equal to 2.0 mg/dl, (vi) serum bilirubin less than twice normal, (vii) no concomitant prior malignancy other than curatively resected *in situ* carcinoma of the cervix or non-melanoma skin cancer, (viii) protime twice normal or less, (ix) no history of recent myocardial infarction, congestive heart failure, arrhythmia or angina, and (x) measurable disease defined as any mass reproducibly measured in two perpendicular dimensions by physical or radiological means. At the time of entry, all patients had the following studies performed: complete blood counts (CBC), differential, electrolytes, BUN, creatinine, AST, ALT, alkaline phosphatase, bilirubin, PT, PTT, TT, urinalysis, EKG, chest X-ray, appropriate CT, MRI and/or bone scan, if applicable. Blood counts were done twice weekly during therapy. Chest X-ray, urinalysis liver function tests, electrolytes, BUN and creatinine were done on day 1 of each course. Tumor measurements were recorded at least every three courses. Warfarin, 1 mg orally each day, was begun on all patients 3 days before or 7 days after Hickman catheter insertion. All patients gave written informed consent and the trial was approved by the Institutional Review Board of the University of Minnesota.

Paclitaxel (IND #43 300) was administered as a constant continuous intravenous infusion, through a centrally placed catheter which allowed *ex vivo* connection with a wearable pump (I-FLOW, Irvine, CA). The first treatment was given as an inpatient to allow monitoring for idiosyncratic toxicity; subsequent 7 day treatments were given as an outpatient. Starting total dose for the first treatment was 120/m^2 (total dose) (17.1 mg/m^2/day) and administered by constant i.v. infusion over 7 days. The first three patients began therapy with 120 mg/m^2 of paclitaxel as a 4 day infusion. The next cohort (five patients) was begun at 120 mg/m^2 as a 7 day infusion. The volume of paclitaxel administered was 480 ml/24 h. Bags containing paclitaxel were changed every 24 h. The patient returned to the clinic monthly for evaluation and initiation of the next treatment cycle. Courses were repeated every 28 days if the absolute neutrophil and platelet counts were greater than or equal to 1500 ml and greater than or equal to 100 000 ml, respectively, on day 1 of each course. Doses were modified based on hematologic and gastrointestinal toxicity. If the nadir absolute neutrophil count (ANC) was greater than or equal to 1200 and the platelet count greater than or equal to 100 000, the paclitaxel dose was increased

10% for the next course. The paclitaxel dose was decreased 10% for a nadir ANC less than or equal to 499 and a platelet nadir greater than or equal to 40 000, or for grade 2 or higher mucositis. If the platelet nadir was less than 40 000, the paclitaxel dose was decreased by 30%. Dose modifications were planned based on renal, hepatic and neurotoxicity, but were not necessary in this study. The severity of hematologic, gastrointestinal and neurologic toxicities were graded according to standard CALGB criteria. Therapy was given as long as tolerated without evidence of disease progression. Standard criteria for objective response to treatment were used in this study.

Subsequent cohorts of five patients each began treatment at 110% of the starting dose of the previous cohort if (i) no more than one of the cohort suffered toxicities that would require a dose reduction for subsequent courses and (ii) no patient experienced grade 4 toxicity (except neutropenia) during the 28 days following initiation of the drug. Data derived from the first course of treatment of each patient were used to determine the MTD. The MTD was defined as the dose that would (i) require dose reduction for a subsequent treatment in no more than one of five patients and (ii) cause no grade 4 toxicity (except neutropenia). When the MTD was reached, the last cohort of patients received a 5% dose reduction from the previous cohort.

Four questions were addressed in this study. (i) What is the MTD for paclitaxel given as a 7 day infusion? (ii) Is outpatient ambulatory treatment feasible, in which the operational definition was 'treatment can be given with a wearable pump in the ambulatory setting without the need for hospitalization in greater than or equal to 80% of the patients'? (iii) What toxicities occur with this schedule of drug administration? (iv) Can activity of this treatment be detected in refractory sarcomas?

Results

Patient characteristics

The ages of the 32 patients in this study ranged from 32–73 years (median 55 years). There were 11 men and 21 women. Eighteen patients had a sarcoma (two malignant fibrous histiocytoma, two synovial sarcoma, 10 leiomyosarcoma, one angiosarcoma, one PNET, one fibrosarcoma and one cystosarcoma phalloides). Three patients had renal cell carcinoma, one a mullerian duct carcinoma, one an adenoid cystic carcinoma, two head and neck cancers, three colon cancers, three non-small cell lung cancers, and one a non-Hodgkin lymphoma.

All patients had a Karnofsky score greater than 40. All patients had previously received chemotherapy. Eighteen patients with sarcoma had received previous chemotherapy for metastatic disease. All patients with soft tissue sarcomas had previously been treated with doxorubicin, dacarbazine, ifosfamide and etoposide.

The first treatment was given in the hospital to monitor for toxicity. No patients required subsequent inpatient treatment, although two received their treatments in hospital for their convenience due to the distance of their residence from our center. Subsequent treatments were given on an ambulatory basis at home using a wearable infusion pump as described in Materials and methods. The number of courses given per patient ranged from 1 to 12 (10 patients received one cycle, 12 received two cycles, two received three cycles, six received four cycles and two received 12 cycles). A total of 88 cycles were given.

Toxicity

All patients completed at least one course of treatment and 29 were evaluable for toxicity. Most patients remained ambulatory and many performed normal activities during chemotherapy infusion. Toxicity was primarily hematological and gastrointestinal.

Hematologic recovery allowed delivery of the treatments every 4 weeks in all patients. Blood counts from 83 cycles were available for analysis. The nadir neutrophil counts ranged from 84 to 2255 cells/ml. In the first 7 day infusion cohort (120 mg/m^2) there was one episode each of central line infection, grade 4 thrombocytopenia requiring platelet transfusion, grade 2 neutropenia, grade 1 neutropenia, grade 1 stomatitis and grade 1 myalgias. In the second cohort (132 mg/m^2) there was one episode each of catheter infection, grade 3 neutropenia, and two episodes of grade 1 fatigue. In the third cohort (145 mg/m^2) there was one catheter infection but no significant hematologic or gastrointestinal toxicity. In the fourth cohort (160 mg/m^2) there was one episode each of grade 4 neutropenia, grade 3 neutropenia, grade 1 nausea and grade 1 fatigue, and three episodes of grade 1 stomatitis. In the fifth cohort (175 mg/m^2) the first two patients experienced grade 4 neutropenia and one experienced grade 4 stomatitis and neutropenic fever, thus terminating entry into this cohort. Of the three patients in the final cohort (167.5 mg/m^2) there was one grade 4 stomatitis, one grade 1 stomatitis, one grade 1 fatigue, one grade 1 diarrhea, one grade 2 neutropenia, two grade 3 neutropenia and one line infection. Platelet counts less than 100 000 were

observed only in the first cohort (120 mg/m^2). Little effect on the hemoglobin concentration was noted. The time to nadir counts ranged from 2 to 3 weeks. No bleeding complications were observed. Nausea occurred in only two patients, both of whom were found to have brain metastases within 3–28 days of entering the study, and antiemetics were not routinely used. The dose modifications for the second treatment are shown for each cohort in Table 1.

Among the 28 courses given at 160/m^2 among all patients regardless of their starting dose, the hematologic and gastrointestinal toxicity are shown in Table 2. In these 28 courses, one episode of grade 1 myalgia, five episodes of grade 1 fatigue and one catheter infection were also observed. No neuropathy was observed in any patient in the study regardless of treatment cycle. Other toxicities, except for alopecia, were not observed at this dose; alopecia was inevaluable as most patients had alopecia from prior therapy. The dose modifications among all patients that received the indicated dose regardless of initial dose (34 cycles) are shown in Table 3.

Neutropenic fever was seen in one of 86 cycles. The central catheter became infected without neutropenia in four cycles, two occurring in the same patient. There were no deaths from toxicity.

Response

Twenty-eight patients were evaluable for response. Of 15 evaluable patients with a soft tissue sarcoma refractory to doxorubicin, ifosfamide, DTIC and etoposide, there were one patient with a partial relapse (PR), five with stable disease (SD), and nine with progressive disease (PD). The PR was maintained for 12 months in a patient with rapidly growing angiosarcoma. Toxicity would have allowed continued dose escalation in this patient, but since a response was observed at the first dose (140 mg/m^2), dose escalation was held at 242 mg/m^2. Among the other evaluable patients a PR was observed in one of two patients with renal cell carcinoma, one of one patient with head and neck cancer, and one of one patient with mullerian duct carcinoma. Of three patients with non-small cell lung carcinoma refractory to cisplatin and etoposide, there was one CR maintained for more that 15 months, one with SD and one with PD. SD was observed with one patient with adenoid cystic carcinoma and one with adenocarcinoma of the parotid gland. Two patients with colon cancer had PD.

Table 1. Dose modification for second treatment

Starting dose (mg/m^2)	Decrease	No change	Increase
120	1	1	3
132	0	0	5
145	0	1	4
160	1	1	3
167.5	1	2	0
175	2	0	0

Dose modifications (as described in Materials and methods) for the second treatment for each cohort. The number of patients in each category is shown.

Table 2. Toxicity of 160 mg/m^2 infusion

	Grade (CALGB scale)				
	0	1	2	3	4
Hematologic					
neutrophils	11	7	2	6	2
platelets	28	0	0	0	0
Gastrointestinal					
nausea	27	1	0	0	0
vomiting	28	0	0	0	0
mucositis	18	10	0	0	0
diarrhea	28	0	0	0	0

CALGB: Cancer and Leukemia Group B. Grade 0: absolute neutrophil count 2000 or higher, platelet count normal; grade 1: absolute neutrophil count 1500–1999, platelet count above 75 000–normal; grade 2: absolute neutrophil count 1000–1499, platelet count 50 000–74 900; grade 3: absolute neutrophil count 500–999, platelet count 25 000–49 900; grade 4: absolute neutrophil count below 500, platelet count below 25 000. Number of cycles (from a total of 28 evaluable cycles) associated with the indicated severity of toxicity.

Table 3. Dose modifications in any treatment of those patients that received a dose

Dose (mg/m^2)	Increase	Decrease	Same
145	7	0	2
160	10	1	4
175	6	2	2

Dose modification (as described in Materials and methods) for subsequent treatments of all patients receiving a course at the indicated dose regardless of starting dose.

Discussion

In vitro studies of paclitaxel suggest a longer exposure to drug results in a greater cell kill. In the present study the MTD for a 7 day continuous infusion of paclitaxel was 160 mg/m^2. The major side effects of a 7 day paclitaxel infusion were neutropenia and mucositis. Other side effects included variable hair loss, some

fatigue, and the inconvenience of wearing an ambulatory pump system and changing the drug reservoir every 24 h. Although 160 mg/m^2 is a reasonable starting dose of paclitaxel for a 7 day infusion, in a heavily pretreated patient population, as studied here, subsequent dose reduction may be required.

A pharmacokinetic and pharmcodynamic analysis of a 3 h versus 24 h infusion of paclitaxel found that the dose-limiting toxicities of the 3 h infusion were peripheral neuropathy and hypotension in addition to granulocytopenia (the dose-limiting toxicity of the 24 h infusion).[11] The MTD of the 3 h infusion was 240 mg/m^2 while the MTD for the 24 h infusion was 180 mg/m^2, and the duration for which the plasma paclitaxel concentration was above 0.05 mM was the common pharmacokinetic parameter that predicted neutropenia with both infusion times.[11] The 120 h infusion study found an MTD of 150 mg/m^2.[12] A study of a 96 h paclitaxel infusion schedule also demonstrated a relationship between neutropenia, mucositis and a serum steady-state concentration above 0.07 mM;[7] there, the MTD was 160 mg/m^2 and 140 mg/m^2 was selected for subsequent phase II studies. While the time during which the plasma level of paclitaxel is above a critical level (above 0.05-0.1 uM) is an important determinant of the degree of neutropenia,[3,7,11] the pharmacologic determinants of tumor response are not clearly defined.

When the present study was initiated, paclitaxel solutions were known to be stable for 24 h at 23°C,[13] providing the basis for our study design in which bags of paclitaxel were changed every 24 h. More recent studies have found that solutions of paclitaxel at 0.3-1.2 μg/ml are stable in containers for at least 48 h,[14] suggesting that in future studies the paclitaxel bags could be changed every 48 h, simplifying treatment for the patient, and decreasing pharmacy and material costs. Based on results of studies of other infusional studies, it is likely that premedication is not needed with a 7 day infusion, although premedication was used in the current study.

In the current study, one of 15 patients with a chemotherapy refractory soft tissue sarcoma, here an angiosarcoma, obtained a PR that persisted for 12 months. The response rate of soft tissue sarcomas to chemotherapy appears to relate to tumor grade;[15,16] of note, five of 15 of the evaluable patients with soft tissue sarcoma in the current study were low grade sarcomas. In a phase II study of 48 patients with soft tissues sarcoma treated with a 24 h infusion of 250 mg/m^2 paclitaxel, six responses were observed (95% CI, 4.7-25.3%).[17] In that study, like the present study, a high percentage of patients had leiomyosarcomas, which could contribute to a low response rate. In contrast to this study of paclitaxel at 250 mg/m^2 over 24 h in which grade 4 toxicity was frequent,[17] in the current study a 7 day infusion at 160 mg/m^2 was generally well tolerated. In another study of 28 patients with soft tissue sarcomas receiving paclitaxel at 250 mg/m^2 over 3 h, two of two patients with angiosarcoma had a major response.[18] These results are intriguing and suggest that further studies of infusional paclitaxel may be appropriate in patients with high grade sarcomas.

Conclusions

We conclude that paclitaxel given by ambulatory continuous i.v. infusion over 7 days is well tolerated with a maximally tolerated starting dose of 160 mg/m^2. The major side effects of a 7 day paclitaxel infusion were neutropenia and mucositis. Nausea and neurotoxicity were rare. Further studies of infusional paclitaxel may be appropriate in patients with high grade sarcomas.

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