Phase I Clinical Trial of Weekly Combined Paclitaxel plus Docetaxel in Patients with Solid Tumors

Jacob Lokich, M.D.

Department of Neoplastic Disease, The Cancer Center of Boston, Boston, Massachusetts.

Presented in part at the Chemotherapy Foundation Symposium, November 1999

Supported in part by The Cancer Center Research Foundation.

Address for reprints: Jacob Lokich, M.D., The Cancer Center of Boston, 125 Parker Hill Avenue, Boston, MA 02120; Fax: (617) 739-4819; E-mail: jlokich@cancercenter-of-boston.com

Received January 21, 2000; revisions received June 23, 2000, and July 28, 2000; accepted July 28, 2000.

BACKGROUND. A Phase I and feasibility study of combined docetaxel (D) plus paclitaxel (P) was undertaken to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) for each analogue delivered concomitantly on a weekly schedule.

METHODS. Patients were accrued in 3–6 patient cohorts to P administered over a course of 45–60 minutes followed by D infused over a course of 30 minutes for 4 consecutive weeks with the cycles repeated at 6 weeks. The MTD was defined as the dose of each agent administered with at least Grade 3 (according to National Cancer Institute standard criteria) hematologic toxicity in 50% of the patients but without Grade 4 toxicity.

RESULTS. Twenty patients received D plus P weekly for 4 weeks at 4 dose levels. At the highest P dose (80 mg/m^2; total dose per cycle, 320 mg/m^2) 2 of 6 patients received treatment for 4 consecutive weeks but 5 of 6 patients developed hematologic and/or nonhematologic (skin) DLTs. The recommended treatment doses for this combined taxane regimen is D, 35 mg/m^2/week, plus P, 65 mg/m^2/week, for 4 weeks. An unusual cutaneous syndrome was observed in four patients that was manifested as erythema and blistering on the dorsum of the hands.

CONCLUSIONS. The lack of complete cross-resistance for D and P in experimental systems and the clinical observation that tumor resistance to one taxane does not necessarily convey resistance to the alternative taxane was the basis for exploring the use of both analogues administered simultaneously. This Phase I trial establishes the optimal weekly dose for each taxane when administered in combination.
***Cancer* 2000;89:2309–14.** *© 2000 American Cancer Society.*

KEYWORDS: paclitaxel, docetaxel, solid tumors, Phase I clinical trial, maximum tolerated dose, dose-limiting toxicity.

Combining analogues together as a multidrug regimen has been explored with the podophyllotoxin analogues,[1] the platinum analogues,[2,3] and the anthracycline-type drugs.[4] The rationale for combining antineoplastic analogues is based on increasing the drug concentration to achieve the maximum lethal cellular effect by the specific cytotoxic mechanism shared by the related compounds. The ability to administer both analogues concomitantly is critically dependent on the drugs having different toxicity profiles so that the maximum single agent dose for each agent can be delivered. If the analogue agents do not overlap in terms of cross-resistance, an additional advantage of combining two related drugs within a class is to affect potentially the neoplastic cells resistant to the other analogue.

Paclitaxel and docetaxel are two members of the taxane family of drugs, in which the mechanism of cytotoxicity for both agents is related to stabilizing and preventing the depolymerization of tubulin during mitosis. In experimental systems a lack of complete cross-

resistance in some multiple cell lines can be demonstrated[5] and in some clinical trials it has been shown that patients resistant to one taxane may respond to the alternative taxane.[6,7] In addition, the nonhematologic toxicity profile for each of the taxanes is different and also may differ according to the schedule of taxane administration.

Based on the fact that there is incomplete cross-resistance for the two taxanes and that the nonhematologic toxicity profiles are different, we initiated a Phase I clinical trial in which both taxanes were administered concomitantly on a weekly schedule with the objective of establishing whether the total delivered dose of taxane could be increased over that achieved with either agent alone and to establish the toxicity profile and dose-limiting toxicity (DLT) for the simultaneous administration of both agents. Secondary objectives of the study included assessment of the use of a special application of granulocyte cytokine administration to maintain the dose and schedule for taxane delivery.

MATERIALS AND METHODS

Between October 1998 and April 1999, 20 patients were entered into this Phase I feasibility study. All patients had biopsy proven advanced malignancy and informed consent was obtained from all patients. Entry criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2, a life expectancy of at least 3 months, a leukocyte count of > 3000 cells/μL, and a platelet count $> 150{,}000$ cells/μL; normal liver function tests and a serum creatinine concentration < 1.5 mg/dL also were required.

The study was conducted using a standard Phase I design with cohorts of patients entered and receiving a fixed dose of docetaxel with escalation of the dose of paclitaxel. Dose escalation within patients was permitted and a minimum of three patients were scheduled to be entered at each dose level. The weekly schedule was selected based on multiple previous Phase I and Phase II studies establishing the optimal weekly dose for each taxane.[8-18] Initial patients received a fixed dose of docetaxel, 30 mg/m^2. This was preceded by the dose of paclitaxel, which was escalated from a baseline dose of 50 mg/m^2/dose to 65 mg/m^2 and then 80 mg/m^2. After the maximum tolerated dose (MTD) was reached for the paclitaxel component, the next lower level of paclitaxel was combined with an escalated dose of docetaxel to form Cohort 4. Paclitaxel was administered over 60 minutes and docetaxel was administered over 30 minutes. Doses were repeated at weekly intervals for 4 weeks with the cycles repeated at 6 weeks as an arbitrarily selected schedule.

The MTD was defined as that individual dose for paclitaxel and docetaxel that permitted the completion of a 4-week dose cycle with Grade 3 or 4 hematologic toxicities developing in $\leq 50\%$ of cycles with or without the use of concomitant granulocyte-colony stimulating factor (GCSF). At the MTD, nonhematologic toxicity could be no higher than Grade 3 in any patient.

No patients received premedication to prevent docetaxel-related edema and no patients received premedication for the prevention of hypersensitivity reactions. Antiemetics also were not used routinely but only at the discretion of the primary physician. The rationale for not using the recommended dexamethasone prophylaxis for edema and the H_1 and H_2 blockers for hypersensitivity reaction prophylaxis was based on avoiding adverse corticosteroid effects and the fact that, in our experience, these episodes are uncommon to rare.

Cytokine usage was guided by previous reported experience using single-dose GCSF concomitant with the fractionated dose of chemotherapy.[19] In the schema, GCSF, 480 μg, was administered subcutaneously in patients in whom the leukocyte count was between 1000–3500/mm^3. The dose of chemotherapy was deleted only for patients in whom the leukocyte count had fallen below 1000/mm^3. This pattern of usage for GCSF cytokine has been successful in maintaining the dose intensity in other taxane-related programs at The Cancer Center of Boston.[20,21]

Toxicity was graded using the standard criteria established by the National Cancer Institute (NCI) guidelines for both hematologic and nonhematologic toxicity. Tumor response criteria for complete and partial responses as well as criteria for progressive disease also followed standard response criteria guidelines from the NCI. Complete response indicated 100% resolution of all measurable disease and partial response reflected a 50% decrease in the product of the perpendicular dimensions of the measurable disease. All other changes (or stability) were considered to be in the category of no response.

RESULTS

Twenty patients received a total of 26 cycles of therapy. Table 1 lists the demographic characteristics of the 20 patients and the spectrum of tumors that were treated. Approximately 50% of the patients had received prior single-agent taxane therapy. One patient was ineligible on the basis of ECOG performance status but was included in the data.

Table 2 outlines the total patient entry experience, focusing on the four individual patient cohorts. At the starting dose of paclitaxel, 50 mg/m^2, and docetaxel,

TABLE 1
Demographic Profile of Patients

No. of patients	20
Male/female	13/7
Age (yrs), median (range)	66 (44–85)
Prior chemotherapy	11
Prior taxane	10
Prior radiation	12
Tumor types	
Prostate	4
Pancreatic	2
Gynecologic	3
Gastric	4
Lung	2
Unknown primary	1
Renal	2
Hepatocellular	2
ECOG performance status	
0, 1	16
2	3
3, 4	1

ECOG: Eastern Cooperative Oncology Group.

30 mg/m^2, 6 patient entries resulted in 3 completed cycles for a completion rate of 50%. Of the three patients not completing the entire cycle, two had received major prior radiation or a prior bone marrow transplant and one patient developed Grade 3 stomatitis. Dose escalation was undertaken considering that the three "good risk" patients had no hematologic or nonhematologic toxicities. Three of six patients in the second cohort completed all four doses within the cycle. The other three patients had no DLTs but declined additional therapy. In the third patient cohort, two patients did complete the total of four doses but a nonhematologic DLT developed subsequently in the form of a drug rash. In the fourth cohort of patients the dose of paclitaxel was reduced to the second cohort level and the dose of docetaxel was increased. At this dose level, 7 of 8 cycles (87%) were completed, 2 of which utilized single-dose GCSF to maintain the blood counts and dose schedule.

A cutaneous toxicity was observed with this regimen that was believed to be related to dose of administration. Five patients experienced a cutaneous toxicity syndrome that was geographically specific. Erythema developed over the metacarpal phalangeal joints and over the dorsum area between the thumb and index finger and the lateral hypothenar eminence and simultaneously in the periarticular area of the ankle. The cutaneous toxicity was associated with vesicles and blister formation and resolved with the interruption of therapy. Dose reduction of the paclitaxel in a subsequent cycle prevented the reappearance of the cutaneous toxicity.

Table 3 summarizes the total toxicity experience in terms of Grade 2, 3, and 4 hematologic and nonhematologic toxicities. Four Grade 4 and four Grade 3 hematologic toxicities were observed and in Cohort 3 (at the highest dose level of paclitaxel), two patients experienced neutropenic fever requiring hospitalization. Stomatitis was infrequent as was diarrhea, with the majority of nonhematologic toxicities prominent only at the highest paclitaxel dose.

Utilizing single-dose GCSF in the treatment of the leukopenia observed in conjunction with the weekly schedule of double taxane combination chemotherapy, the recommended doses of the individual agents using a weekly $\times$ four cycle was paclitaxel, 65 mg/m^2/dose, and docetaxel, 35 mg/m^2/dose. For poor risk patients who 1) have received extensive prior chemotherapy, 2) are elderly, or 3) have received prior bone marrow-exposed radiation, the recommended dose is paclitaxel, 50 mg/m^2/fraction, and docetaxel, 30 mg/m^2/fraction.

Responses were observed in 1 patient with gastric carcinoma who had received a prior paclitaxel-based regimen and 3 of 4 patients with prostate carcinoma were found to have a $>$ 50% decrease in their prostate specific antigen level, one of whom had regression of liver metastases. No other patients achieved an objective measurable response to the therapy.

DISCUSSION

Combining analogues within a class of antineoplastic drugs previously has been reported using the epipodophyllotoxins,[1] the platinum analogues,[2,3] and the anthracyclines.[4] The rationale for this concept is to increase the dose of the cytotoxic principle drug, but it must be acknowledged that to our knowledge none of the studies evaluated to date combining analogues within a class have demonstrated an increase in efficacy using this strategy. Paclitaxel and docetaxel are two members of a class of drugs known as the taxanes (or taxoids) and although the two analogues share a number of chemical characteristics and mechanisms of cytotoxicity, they also differ in many aspects (Table 4) related to relative potency, schedule dependency, and clinical toxicity. Furthermore, the two drugs lack cross-resistance in in vitro cytotoxicity.[5] Although the major DLT for both agents is leukopenia, the toxicity profiles for the two drugs differ in many other respects. In particular, the toxicity profile for paclitaxel is associated with myalagia, stomatitis, and neuropathy and docetaxel is associated most commonly with fluid retention and asthenia.

The current study concept of combining the two taxanes to be administered simultaneously as a "taxane package" was conceptualized on the basis of the

TABLE 2
Proportion of Four Weekly Treatment Fractions Completed Related to Dose Level

	Dose mg/m^2/Fx		Total dose/cycle			
Cohort	P	D	P	D	Cycles	No. of cycles completed
1	50	30	200	120	7	3 (50%)[a]
2	65	30	250	120	6	3 (50%)[b]
3	80	30	320	120	6	2 (33%)
4	65	35	260	140	8	7 (87%)

Fx: fractions; P: paclitaxel; D: docetaxel.

[a] Of the three patients not completing all four fractions, two had Grade 3 leukopenia after only one and two fractions, respectively, related to prior radiation and prior bone marrow transplantation; one patient had mouth sores after three fractions.

[b] None of the three patients not completing four fractions had a dose-limiting toxicity; one patient developed a skin rash and two patients declined further therapy after two and three doses, respectively.

TABLE 3
Grade 2, 3, and 4 Toxicity Profiles by Cohort Dose[a]

Cohort	Leukopenia[b]	Skin rash[c]	Diarrhea	Stomatitis	Asthenia
1	2 Grade 3; 1 Grade 4	1 Grade 3	0	2 Grade 2	0
2	1 Grade 3	1 Grade 4	0	0	1 Grade 2
3	1 Grade 3; 2 Grade 4	2 Grade 3	2 Grade 3	2 Grade 2	4 Grade 3
4	1 Grade 4	1 Grade 3	2 Grade 2	0	2 Grade 2

[a] Grading performed according to National Cancer Institute Standard criteria.

[b] Two patients developed febrile neutropenia and required hospitalization.

[c] Skin rash was maculopapular on the forearms, torso, and face with erythema and blister formation on the skin over the metacarpal phalangeal articulations and to a lesser extent on the plantar surfaces of the feet and the skin of the periarticular area around the heel.

TABLE 4
Differences between Docetaxel and Paclitaxel

Parameter	Docetaxel	Paclitaxel
Binding affinity for Beta-tubulin	1.9[a]	1.0
Binding sites for Beta-tubulin	Tau	N-terminal 31 amino acids
Depolymerization inhibition	2[a]	1.0
Mitotic structure	Centrozome	Mitotic spindle
Cell cycle specificity	S-phase	G_2/M-phase

[a] Relative potency compared with paclitaxel.

Adapted from data provided through the courtesy of RPR Pharmaceuticals.

lack of an overlap of nonhematologic toxicities between the two drugs and anecdotal clinical data that indicate that a proportion of patients who develop a resistance to one taxane may be responsive to the alternative taxane. By combining the two analogues, one potentially could increase the cumulative taxane dose and achieve an accentuation of the primary mechanism of cytotoxicity (i.e., inhibition of depolymerization of the mitotic spindle), although clinically there is no evidence that increasing the dose of taxane above the threshold level increases the response rate.[22]

This Phase I study indicates that the total taxane dose per week may be increased modestly by combining the two taxanes. It has been established that a weekly schedule can increase the MTD for each individual taxane when compared with the every 3-weeks dosing schedule. Thus, for example, the every 3-weeks schedule dose of single agent paclitaxel yields a dose intensity of approximately 58 mg/m^2/week compared with a dose of 90–100 mg/m^2/week utilizing the weekly schedule. Some studies have demonstrated that the dose of 100 mg/m^2/week can be increased to as much as 175 mg/m^2/week but general usage is approximately 100 mg/m^2/week or slightly less. For docetaxel, the every 3-weeks dosing schedule yields a dose intensity of 33 mg/m^2/week (100 mg/m^2/cycle) compared with a dose intensity of 35 mg/m^2/week or up to 42 mg/m^2/week utilizing a weekly schedule.

With the combined taxane program, the dose intensity of docetaxel is maintained at 35 mg/m^2/week and paclitaxel can be added at a dose of 65 mg/m^2/cycle or 65% of the generally employed weekly dose of single agent paclitaxel (100 mg/m^2). Therefore, the overall taxane dose intensity is increased by a factor of 1.65 when the 2 taxanes are combined. In addition to increasing the taxane cytotoxic injury by using the two agents together, one may hope to take advantage of

the fact that the agents lack complete cross-resistance in some tumors such that paclitaxel nonresponders may be affected by the availability of docetaxel and vice versa.

An important aspect of the execution of the current study involved the unique use of granulocyte cytokine support to permit the weekly schedule of the administration of both drugs. The concomitant use of GCSF simultaneously with chemotherapy dosing and triggered by specific leukocyte count parameters has been reported and tested in previous studies of paclitaxel-based clinical trials from The Cancer Center of Boston.[19-21] Paclitaxel using the traditional every 3-weeks schedule typically induces a sharp nadir at 7–10 days that recovers within 2 days. Because the nadir leukopenia is quite narrow, the need for protracted daily dosing of GCSF to protect against neutropenic fever may be unnecessary. The goal of the concomitant administration of GCSF with weekly dual taxane administration was to maintain the treatment schedule. In the current study, five patients received GCSF at dose Fraction 2 or 3 to maintain a leukocyte count sufficient to continue therapy; this was successful in all five patients.

The toxicity profile for the double taxane treatment administered on a weekly schedule was consistent with the known toxicities observed with the two agents with the exception that fluid retention was not observed in any patient although only a few patients received four or more cycles. In addition, no nausea or emesis was observed in spite of the lack of pretreatment antiemetics. One minor hypersensitivity reaction was observed but with that exception, there were no other episodes despite the fact that neither H_1 or H_2 blockers or corticosteroids were used. Five patients did experience an unusual pattern of skin rash over the hands and feet and all patients receiving two or more cycles experienced nail changes that previously have been reported in association with taxanes. The hand changes appeared predominantly over the dorsum of the hands, especially over the metacarpal pharyngeal articulations and with rather striking erythema and vesicle formulation. In addition, some patients experienced blister formation on the palms and soles similar to the hand-foot syndrome associated with the protracted infusion of 5-fluorouracil. To our knowledge the mechanism of skin cytotoxicity is unclear, as is a means of prevention.

This Phase I study establishes the optimal doses for paclitaxel and docetaxel when employed concomitantly utilizing a weekly schedule and establishes the capability of increasing taxane exposure by this strategy. Whether the modest increase in taxane dose would translate into a meaningful increment in tumor cell killing is unknown and to our knowledge no studies to date have shown such an effect. However, an additional rationale for combined taxane use is the lack of complete cross-resistance for the two agents such that one taxane would affect the neoplastic cells resistant to the alternative taxane and vice versa. The utility of this approach to taxane chemotherapy in terms of therapeutic efficacy would necessitate Phase II trials and eventually Phase III comparative trials of the single agent taxane with the combined taxane doublet.

REFERENCES

1. Allen LM. Tajada F, Okonmah AD, Nordquist S. Combination chemotherapy of the epipodophyllotoxin derivatives, teniposide and etoposide. A pharmacodynamic rationale? *Cancer Chemother Pharmacol* 1982;7:151–6.
2. Piccart MJ, Nogaret JM, Marcelis L, Longree H, Ries F, Kains JP, et al. Cisplatin combined with carboplatin: a new way of intensification of platinum dose in the treatment of advanced ovarian cancer. *J Natl Cancer Inst* 1990;82:703–7.
3. Soulie P, Bensmaine A, Garrino C, Chollet P, Brain E, Fereres M, et al. Oxaliplatin/cisplatin (L-OHP/CDDP) in combination in heavily pretreated ovarian cancer. *Eur J Cancer* 1997; 33(9):1400–6.
4. Stewart DJ, Perrault DJ, Maroun JA, Lefebre BM. Combined mitoxantrone plus doxorubicin in the treatment of breast cancer. *Am J Clin Oncol* 1987;10:335–40.
5. Verweij J, Claveli M, Chevalier B. Paclitaxel (taxol) and docetaxel (taxotere): not simply two of a kind. *Ann Oncol* 1994;5:495–5.
6. Valero V, Jones SE, Von Hoff DD, Booser DJ, Mennel RG, Ravdin PM, et al. A phase II study of docetaxel in patients with paclitaxel-resistant metastatic breast cancer. *J Clin Oncol* 1998;16:3362–8.
7. Androulakis N, Kouroussis C, Kakolyris S, Tzannes S, Papadakis E, Papadimitriou C, et al. Salvage treatment with paclitaxel and gemcitabine for patients with non small cell lung cancer after cisplatin-or docetaxel-based chemotherapy: a multicenter phase II study. *Ann Oncol* 1998;9:1127–30.
8. Tomiak E, Piccart MJ, Kerger J, Lips S, Awada A, de Valeriola D, et al. Phase I study of docetaxel administered as a 1-hour intravenous infusion on a weekly basis. *J Clin Oncol* 1994; 12:1458–67.
9. Hainesworth JD, Burris HA, Erland JB, Thomas M, Greco FA. Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer. *J Clin Oncol* 1998; 16:2164–7.
10. Luck HJ, Donne S, Glaubitz M, Kuhnle H, Merhenke P, Welker T, et al. Phase I study of weekly docetaxel (Taxotere) in heavily pretreated breast cancer patients. *Eur J Cancer* 1997;33:S158.
11. Loeffler TM, Freund W, Droge C, Hausamen TU. Activity of weekly Taxotere (TXT) in patients with metastatic breast cancer. *Proc Am Soc Clin Oncol* 1998;17:113a.
12. Fennelly D, Aghajanian C, Shapiro F, O'Flaherty C, Mckenzie M, O'Connor C, et al. Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. *J Clin Oncol* 1997;15:187–92.

13. Seidman AD, Murphy B, Hudis C, McCaffrey C, Tong J, Currie W, et al. Activity of taxol by weekly 1-hour infusion in patients with metastatic breast cancer. A phase III and pharmacologic study. *Proc Am Soc Clin Oncol* 1997;16:148A.
14. Ackerly W, Glantz M, Choy H, Rege V, Sambandam S, Joseph P, et al. Phase I trial of weekly paclitaxel in advanced lung cancer. *J Clin Oncol* 1998;16:153–8.
15. Arbuck SG, Canetta R, Onetto N, Christian MC. Current dosage and schedule issues in the development of paclitaxel (TAXOLr). *Semin Oncol* 1993;20(4):31–9.
16. Sikov W, Ackerly W, Strenger R, Cummings F. Weekly high dose paclitaxel (P) demonstrates significant activity in advanced breast cancer [abstract 432]. Proc Am Soc Clin Oncol 1998;
17. Asbury R, Chang A, Boros L, Asbury R, Rubins J. Weekly moderate dose paclitaxel (P) in advanced breast cancer [abstract 486]. *Proc Am Soc Clin Oncol* 1998;
18. Breier S, Lebedinsky C, Ayiviri C, Roffe C, Traine G, Cot C, et al. Long term weekly paclitaxel (P) in metastatic breast cancer (MBC). A phase II trial in pretreated patients (PTS) [abstract 740]. *Proc Am Soc Clin Oncol* 1998;
19. Lokich J. Single-dose granulocyte colony-stimulating factor concomitant with multifractionated dose chemotherapy: a strategy for maintaining dose intensity. *Cancer Invest* 1999; 17(7):547–50.
20. Lokich J, Anderson N, Bern M, Coco F, Gotthardt S, Oliynyk P, et al. Paclitaxel, cisplatin, etoposide combination chemotherapy: a multifractionated bolus dose schedule for non-small cell lung cancer. *Eur J Cancer* 1998;34:659–63.
21. Lokich J, Anderson N, Bern M, Coco F, Dow E. The multifractionated, twice-weekly dose schedule for a three-drug chemotherapy regimen. A phase I-II study of paclitaxel, cisplatin and vinorelbine. *Cancer* 1999;85:499–503.
22. Winer E, Berry D, Duggan D, Henderson IC, Cirrincione C, Cooper R, et al. Failure of higher dose paclitaxel to improve outcome in patients with metastatic breast cancer—results from CALGB 9342 [abstract 388]. *Proc Am Soc Clin Oncol* 1998;