The Multifractionated, Twice-Weekly Dose Schedule for a Three-Drug Chemotherapy Regimen

A Phase I–II Study of Paclitaxel, Cisplatin, and Vinorelbine

Jacob J. Lokich, M.D.
Norwood Anderson, M.D.
Murray Bern, M.D.
Frank Coco, M.D.
Edward Dow, M.D.

The Cancer Center of Boston, Boston, Massachusetts.

BACKGROUND. Paclitaxel, cisplatin, and vinorelbine are three important antineoplastic drugs with different mechanisms of cell kill. A combination of these three drugs potentially could have additive therapeutic effects.

METHODS. The three-drug combination (designated TPN) was administered on a twice-weekly (Monday/Thursday; Tuesday/Friday) schedule for 3 weeks, with cycles repeated every 28 days. The Phase I design utilized a dose de-escalation schema in which the maximum tolerated dose was defined by a patient's ability to complete 6 doses (a full cycle) without interruption for hematologic Grade 3 or 4 toxicity.

RESULTS. Twenty-seven patients received a total of 42 evaluable courses of the 3-drug regimen. The cisplatin dose was fixed at 15 mg/M^2/fraction. The paclitaxel dose was first fixed at 50 mg/M^2/fraction, and venorelbine was delivered at 3 dose levels per fraction: 10, 7.5, and 5 mg/M^2. Paclitaxel then was de-escalated to 40 mg/M^2/fraction, and the same 3 dose levels of vinorelbine were evaluated. The dose-limiting toxicity was neutropenia. Using fixed doses of paclitaxel at 40 mg/M^2/fraction and cisplatin at 15 mg/M^2, the optimal dose fraction for vinorelbine was 7.5 mg/M^2, defined as the dose that allowed $>$ 67% of patients to complete 3 weeks (6 consecutive doses) of therapy. Using paclitaxel at 50 mg/M^2/fraction (cisplatin at 15 mg/M^2/fraction), the optimal dose of vinorelbine was 5 mg/M^2/fraction. Tumor responses were observed in 13 patients: 2 with unknown primary, 1 with esophageal carcinoma, 6 with nonsmall cell lung carcinoma, and 3 with breast carcinoma. Grade 2 neurologic (sensory) toxicity was observed in 5 patients.

CONCLUSIONS. TPN administered according to a twice-weekly dosing scheme can be delivered with acceptable toxicity. The dose intensity for paclitaxel (60–75 mg/M^2/week), cisplatin (22 mg/M^2/week), and vinorelbine (15 mg/M^2/week) is $>$ 50% of the single agent dose intensity for the component agent. Recommended Phase II or Phase III trials could utilize dose fractions of paclitaxel, cisplatin, and vinorelbine at either 50, 15, and 5 mg/M^2/fraction or 40, 15, and 7.5 mg/M^2/fraction in this twice-weekly, multifractionated dose schedule. ***Cancer* 1999;85: 499–503.** © *1999 American Cancer Society.*

KEYWORDS: multifractionated, dose intensity, dose schedule, paclitaxel, cisplatin, vinorelbine.

Multifractionated dosing (MFD) for chemotherapy may be defined as the weekly or biweekly administration of antineoplastic drugs. The rational for this schedule is based on the possibility of increasing the therapeutic effect by more frequent tumor cell exposure and reducing acute drug toxicity as a consequence of decreasing drug dose per fraction. In addition, using MFD, the frequency of severe toxicities may be minimized by real time monitoring which permits

Supported in part by The Cancer Center Research Foundation.

The authors acknowledge, with appreciation, the nursing staff and administrative staff of The Cancer Center of Boston.

Address for reprints: Jacob J. Lokich, M.D., The Cancer Center of Boston, 125 Parker Hill Avenue, Boston, MA 02120.

Received May 26, 1998; accepted July 6, 1998.

interruption or delay of dose fractions at an earlier or lower grade toxicity. Single agent trials have employed MFD schedules for many important chemotherapeutic agents including paclitaxel (T), cisplatin (P), and vinorelbine (N). MFD also has been applied to combination chemotherapy (e.g., with T, P, and etoposide [E]), with a substantial response rate in a spectrum of tumors including lung carcinoma and esophageal carcinoma.[1,2] T, P, and N are active single agents in nonsmall cell lung carcinoma and the two-drug combinations of T and P,[3] T and N,[4,5] and P and N[6,7] have been studied.

In the current study we report the results of a Phase I trial of the three-drug TPN regimen using twice-weekly bolus treatment to determine the maximal dose fraction for the individual components of the regimen. Additional goals were to determine whether inordinate neurotoxicity could be avoided by using this schedule and to develop a basis for a Phase II trial of this combination in patients with nonsmall cell lung carcinoma.

PATIENTS AND METHODS

Patient Eligibility

Patients with histologically or cytologically confirmed advanced disease who were age $>$ 18 years were eligible. All patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of $<$ 2. Patients with prior chemotherapy or radiation were eligible if $\geq$ 3 weeks had elapsed from the time of last therapy. Adequate hematologic (leukocyte count $\geq$ 4000/uL and a platelet count $\geq$ 100,000/uL) function was required as was a serum creatinine level $<$ 1.5 mg/dL and bilirubin $<$ 1.5 mg/dL. Patients with brain metastases were eligible unless active neurologic signs or symptoms were present that required urgent radiation therapy.

Pretreatment evaluation was comprised of a complete history and physical examination, chest X-ray, complete blood cell count, and serum chemistry analysis including a liver profile. Computerized tomography (CT) scans of the chest, abdomen, and pelvis as well as radionuclide bone scans were performed when clinically indicated. CT scans of the central nervous system were obtained when brain metastases were suspected. All pretreatment studies were performed within 4 weeks of initiation of treatment and were repeated prior to every other treatment cycle. Written informed consent was obtained from the patients prior to the initiation of therapy.

Treatment Regimen

The treatment regimen was comprised of the administration of all three agents (T, P, and N) twice weekly for 3 weeks followed by a 1-week hiatus with cycles repeated at 4-week intervals. All treatments were administered either Monday/Thursday or Tuesday/Friday based on the concept of prolonging exposure time to the agents, enabling observation of drug effect from the prior dose. No consecutive day dosing was permitted.

T was administered first in the sequence at a dose of 40 or 50 mg/M^2 infused in 250 mL of normal saline over 1 hour. The P dose of 15 mg/M^2/fraction was fixed and was administered as the second drug in the sequence over 30 minutes. N was administered at 1 of 3 dose fractions (5, 7.5, or 10 mg/M^2) over 10–15 minutes. Although the drug sequence of administration may play a role in determining toxicity and efficacy, the sequence of administration for the TPN combination was arbitrary and generally was given as N followed by T and P. Antiemetics were administered at the discretion of the primary physician but generally included the use of oral granisetron (2 mg) with or without dexamethasone (5 or 10 mg intravenously). Based on previous Cancer Center of Boston experience with a similar MFD schedule utilizing T in which T-associatd hypersensitivity reactions were not observed despite the omission of prophylactic steroids and histamine bloackage, routine administration of dexmethasone, cimetidine, and diphenhydramine was not employed.[8]

Phase I Experimental Design

Patients were entered in cohorts of three at two dose levels for T within which three dose levels of N were evaluated. The objective was to establish the maximum tolerated dose (MTD) of T in the three-drug regimen and the MTD of N within the same three-drug regimen. It was anticipated that the dose-limiting toxicity would be hematologic and that the MTD for T and N would be interdependent such that increasing the dose of one would necessitate a lower dose of the other.

The starting dose of T was fixed at 50 mg/M^2/fraction and N was de-escalated from 10 to 7.5–5 mg/M^2/fraction. The MTD of N then was established. The dose of T then was de-escalated to 40 mg/M^2/fraction with the dose of N deescalated through the same 3 dose levels per fraction. This design for a Phase I trial is particularly useful with the MFD schedule. The starting dose for an agent is selected based on the single agent dose administered on the usual schedule for the agent (weekly for N and every 3 weeks for T) and divided over the twice-weekly 3-week cycle.

The goal was to establish the MTD for both agents that would permit a) 6 consecutive dose fractions administered twice-weekly for 3 weeks and b) achieve at

TABLE 1
Demographic Features of 26 Patients Receiving TPN

Total no. of patients	26
Age (yrs) (median) (range)	65 (43–84)
Gender (M/F)	34:12
Tumor categories	
Lung carcinoma	18
Breast	3
Esophagus	1
Unknown primary	3
Hepatoma	1
Prior therapy	
None	11
Radiation	12
Chemotherapy	13
ECOG performance status	
0–1	15
2	11
Metastatic sites	
Liver	5
Bone	5
Lung	4
CNS	2
Other (lymph nodes)	2

TPN: paclitaxel, cisplatin, and vinorelbine; M: male; F: female; ECOG: Eastern Cooperative Oncology Group; CNS: central nervous system.

least Grade 3 hematologic toxicity (ECOG grading system) in 33% of the patients entered. Therefore, dose fraction interruptions for any cause or any Grade IV hematologic toxicity exceeded the MTD. The specific starting doses for T were selected based on prior single agent MFD studies yielding a dose intensity of 80–100 mg/M^2/week.[1] Dose levels for N were selected based on the dose intensity of a weekly dose schedule of 20 mg/M^2/week. Although the N dose generally is 30 mg/M^2/week, at least 1 study demonstrated that dose adjustments are necessary to the degree that the actual received dose is closer to 20 mg/M^2/week.[9]

RESULTS

Twenty-seven patients were entered on the treatment regimen. One patient experienced a hypersensitivity reaction characterized by hypotension and wheezing, prompting substitution of docetaxel for T and therefore was not included in the toxicity or response data base. Demographic data for the remaining 26 patient entries are listed in Table 1. The major tumor category was nonsmall cell lung carcinoma, within which 10 of 18 patients had Stage IV disease. Nearly half the patients (42%) had received no prior chemotherapy or radiation. Eleven patients (42%) had an ECOG performance status of 2. Forty-two cycles of the 3-drug regimen were initiated; 16 cycles were complete with all 6 dose fractions administered within the cycle. Thirteen of 26 patients received $>$ 1 cycle, with a median of 2 cycles delivered.

The most common toxicity was neutropenia (Table 2). Twenty-three cycles were administered with T fixed at a dose of 50 mg/M^2/fraction. Six of 15 cycles completed the 6-dose fractions of a cycle when the lowest N dose was used and 4 of 15 cycles had Grade 3 (3) or 4 (1) neutropenia developing at the fourth or fifth dose (Days 14–17). At the 2 higher N doses, none of the cycles was completed and 7 of 8 cycles had $\geq$ Grade 3 neutropenia developing (nadir Day 11).

Seventeen cycles were administered with the T dose fraction fixed at 40 mg/M^2/dose. At the highest N dose, no patient completed a treatment cycle with neutropenia nadir occurring at Day 11 for all 3 patient entries. Six of 6 patients (6 of 7 cycles) completed all 6 doses of the cycle at the intermediate N dose of 7.5 mg/M^2/dose. At the lower N dose, only three of seven cycles were completed with four cycles interrupted because of neutropenia (two patients), diarrhea (one patient), and the need for urgent radiation (one patient). Two patients developed neutropenic sepsis and died, one at the highest dose and one at the lowest dose of T and N, respectively.

The maximum T and N doses per fraction are interdependent and to administer all 6 of the doses in a 3-week cycle (along with a fixed dose of cisplatin) paclitaxel at 40 or 50 mg/M^2/dose only can be utilized with a N dose of 7.5 and 5 mg/M^2/fraction, respectively.

In spite of the fact that all three agents may cause neurotoxicity, there was no apparent increase in the frequency or severity of neurotoxicity. Five patients had Grade 2 sensory neuropathy only. This group of 5 patients had received 12–36 doses of TPN with a median cumulative dose for T, P, and N of 960 mg/M^2, 360 mg/M^2, and 180 mg/M^2, respectively. Gastrointestinal toxicity manifested as diarrhea was observed at Grade 2 (three patients) and Grade 3 (four patients), and responded to standard antidiarrhea therapies.

Clinical responses were observed in lung carcinoma (seven partial responses), breast carcinoma (three partial responses), unknown primary tumor (one complete response and one partial response), and esophageal carcinoma (one partial response).

DISCUSSION

T, P, and N are three agents with important activity in a wide spectrum of tumors, particularly lung carcinoma and breast carcinoma. A triplet combination of these three agents could result in improved clinical therapeutic benefit despite the potential for added hematologic and neurologic toxicity, features characteristic of all three drugs as single agents. This Phase I

TABLE 2
Proportion of Patients and Cycles with Development of ≥ Grade 3 Neutropenia on TPN and Proportion Completing Therapeutic Cycle

Dose per fraction of TPN mg/M^2/fraction			No. of patients	No. of cycles	No. of cycles with ≥ Grade 3 neutropenia	No. of completed cycles
50	15	10	3	3	3	0
50	15	7.5	5	5	4	0
50	15	5	9	15	4	6
		Totals	17	23		
40	15	10	3	3	2	0
40	15	7.5	6	7	3	6
40	15	5	6	7	2	3
		Totals	15	17		

TPN: paclitaxel, cisplatin, and vinorelbine.

study of MFD of this three-drug combination was undertaken to establish the optimal dosing of the component agents utilizing a unique MFD scheme.

The triplet combination represents an extension of our previous studies of T, P, and E using MFD. In those studies, it was demonstrated that the dose intensity (DI) of T can be maintained at the level of single agent use by MFD.[1] In addition, clinical activity in lung carcinoma was substantial, with an overall response rate of 75%.[2] In the TPN trial, we replaced the E in the TPE regimen with N, anticipating that N may be more active than E in both lung carcinoma and breast carcinoma. Consequently, we postulated that the TPN triplet may be more active than the previously reported TPE triplet.

This Phase I study focused on a unique schedule of administration for the triplet combination, namely MFD. MFD addresses the issue of the schedule dependency characteristic of many antineoplastic agents while attempting to maximize the DI of the component drugs as measured in mg/M^2/week. The MFD schedule also permits real time monitoring so that Grade 3 and 4 toxicities may be minimized by withholding dose fractions with lower grade toxicity. In contrast, with the traditional intermittent bolus schedule, the drug effect from a committed dose administration may be unpredictably severe. In the TPN combination using the twice-weekly dosing schedule, the DI of N at 10 or 15 mg/M^2/week is lower than that of single agent N, which generally is given as 30 mg/M^2/week although 2 studies have indicated that dose adjustments commonly are required so that the DI is most often at a dose of approximately 20 mg/M^2/week.[7,9] For T and P, the DI at 60–75 mg/M^2 and 22 mg/M^2, respectively, approaches the DI of single agent usage or that of other combinations.

The toxicity profile we observed was predominantly hematologic, with neutropenia and anemia dominating. No significant nausea or emesis was observed but diarrhea was a significant toxicity in a small portion of patients. Neurologic toxicity was expected to be a potent problem but only five patients developed modest sensory neuropathy.

The TPN combination is an especially interesting triplet combining, as it does, drugs that have opposing cellular mechanisms for tumor cell injury (N inhibits microtubular assembly whereas T stabilizes the same process). Furthermore, all three agents have potentially serious neurologic toxicity profiles. Clinical activity for various permentations of two-drug (doublet) combinations have been reported. The combination of T plus N, P plus N, and T plus P have been evaluated in patients with nonsmall cell lung carcinoma[3–7] and responses have varied from 21% (TN) to 30% (NP).

It remains to be established whether the triplet (TPN) is superior to the more commonly used "doublet" of T plus P or carboplatin and the specific role of MFD schedules in effecting therapeutic response and toxicity profiles is another area to be explored in comparative clinical trials. The dose fraction for T and N in the triplet are interdependent in that if T is fixed at a dose of 50 mg/M^2/fraction, the N dose is reduced by 50%. If the T dose is reduced by 20% to 40 mg/M^2, the N dose is increased by 50%. The optimal dose fractions for the 2 agents based on the premise of maximizing the DI of both agents is 40 mg/M^2/dose for T and 7.5 mg/M^2/dose for N.

REFERENCES

1. Lokich J, Anderson N, Moore C, Bern M, Coco F, Sonneborn H, et al. Paclitaxel, cisplatin, etoposide combination chemotherapy: a comparison of dose intensity in two multifractionated dose schemas. *Eur J Cancer* 1998;34:664–7.
2. 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.

3. Sorensen JB, Wedervang K, Dombernowsky P. Preliminary results of a phase II study of Paclitaxel and cisplatin in patients with non small cell lung cancer. *Semin Oncol* 1997; 24:S1218–20.
4. Chang AY, Devore R, Gu C, et al. Paclitaxel and vinorelbine in non-small-cell lung cancer. *Oncology* 1997;11(Suppl 12): 31–43.
5. Breton JL, Jacoulet P, Pellae-Cosset B, et al. Phase I study of paclitaxel (P) over one hour infusion in combination with vinorelbine in advanced non small cell lung cancer (NSCLC) [abstract 302]. *Cancer Conference Highlights* 1997;18(Suppl 1):53.
6. Wozniak AJ, Crowley JJ, Balcerzak SP, et al. Randomized phase III trial of cisplatin vs cisplatin plus navelbine in treatment of advanced non-small-cell lung cancer. Report of a Southwestern Oncology Group study (SWOG 9308) *Proc Am Soc Clin Oncol* 1996;15:374.
7. LeChevalier T, Brisgand D, Douillard J-Y, Pujol J-L, Alberola V, Monnier A, et al. Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non small cell lung cancer: results of a European multicenter trial including 612 patients. *J Clin Oncol* 1994;12:360–7.
8. Lokich J, Anderson N, Bern M, Coco F, Dow E, Moore C, et al. Multi-Day fractionated administration schedule for paclitaxel. *Ann Oncol* 1995;6(9):883–6.
9. Crawford J, O'Rourke M, Schiller JH, Spironidis CH, Yanovich S, Ozer H, et al. Randomized trial of vinorelbine compared with fluorouracil plus leucovorin in patients with stage IV non small cell lung cancer. *J Clin Oncol* 1996;14(10):2774–84.