Am J Clin Oncol (CCT) 20(6): 573–576, 1997.

© 1997 Lippincott–Raven Publishers, Philadelphia

Phase II Trial of Intravenous CI-980 (NSC 370147) in Patients with Metastatic Colorectal Carcinoma

Model for Prospective Evaluation of Neurotoxicity

R. Pazdur, M.D., C. Meyers, Ph.D., E. Diaz-Canton, M.D., J. L. Abbruzzese, M.D., Y. Patt, M.D., W. Grove, M.S., and J. Ajani, M.D.

CI-980 (NSC 370147)—a synthetic mitotic inhibitor that binds to tubulin at the colchicine binding site—has significant activity against a broad spectrum of tumor models and greater in vitro cytotoxicity when given over >24 hours than 4 hours or less. Phase I studies demonstrated central nervous system (CNS) toxicity to be dose-limiting when CI-980 was administered as a 24-hour infusion. When a 72-hour infusion was given, CNS toxicity was reduced and granulocytopenia became the dose-limiting toxicity. In this phase II study, CI-980, 4.5 mg/m^2, was administered as a 24-hour continuous intravenous infusion for 3 consecutive days and repeated every 21 days. Fourteen patients who had measurable metastatic colorectal cancer were entered in the trial. Eight patients had received one prior chemotherapy regimen for metastatic disease. Patients were prospectively monitored by neurologic examinations and neuropsychologic assessment of cognitive functioning. No complete or partial responses were observed. Grade 4 granulocytopenia was the dose-limiting toxicity. Reversible declines in recent memory function were noted in all patients. After each course of CI-980, there were also transient non-significant declines in motor coordination, compared with the preinfusion assessment. At the stated dose and schedule, CI-980 lacks activity in metastatic colorectal carcinoma. The agent's toxicity profile (granulocytopenia and CNS effects) was comparable with previously described effects of this agent.

Key Words: CI-980—Colorectal carcinoma—Colon carcinoma—Rectal carcinoma—Neurotoxicity—CNS toxicity.

From the Department of Gastrointestinal Medical Oncology and Digestive Diseases (R.P., E.D.-C., J.L.A., Y.P., J.A.) and the Department of Neuro-Oncology (C.M.), The University of Texas M. D. Anderson Cancer Center, Houston, Texas , U.S.A.; and Parke-Davis Pharmaceutical Research (W.G.), Division of Warner Lambert Co., Ann Arbor, Michigan, U.S.A.

Supported in part by a contract from Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Co. (Ann Arbor, Michigan, U.S.A.).

Address correspondence and reprint requests to Dr. Richard Pazdur, Division of Medicine, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, U.S.A.

Fluorouracil (5-FU) is the most active agent in the treatment of metastatic colon carcinoma, with response rates of approximately 10% for bolus schedules and 30% for protracted continuous-infusion schedules.[1] Modulation of 5-FU's activity with leucovorin has been extensively investigated. Compared with 5-FU bolus therapy, the combination produces higher response rates, although its effect on survival has not been clearly established.[1] Irinotecan (Pharmacia-Upjohn, Kalamazoo, MI) has recently been approved for the treatment of metastatic adenocarcinoma, having demonstrated response rates of 33% in previously untreated patients and 17% to 27% in previously treated patients but no impact on survival.[2,3] Thus, new agents or treatment strategies for advanced colerectal cancer should be actively investigated.

CI-980, a synthetic mitotic inhibitor that binds to tubulin at the colchicine binding site, inhibits tubulin's polymerization and blocks cell-cycle progression in mitosis.[4] CI-980 is similar to colchicine in structure and function but unlike the latter, also crosses the blood–brain barrier (Fig. 1). CI-980 has significant activity against a broad spectrum of tumor models and retains activity against a panel of tumor models that are cross-resistant to vincristine, vinblastine, navelbine, and doxorubicin.

CI-980 exhibited marked schedule dependency in vitro. With extended exposure (>24 hours), the inhibitory concentrations were thousands of times lower than inhibitory concentrations at short exposures (<4 hours). In contrast, the cumulative maximum tolerated dose in vivo was relatively constant, regardless of the regimen used. Preclinical animal toxicology studies in Wister rats demonstrated dose-related reversible myelosuppression and testicular tubular degeneration. These studies did not reveal neurotoxicity, even at approximately lethal doses.[5]

Two phase I protocols with CI-980 have been con-

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

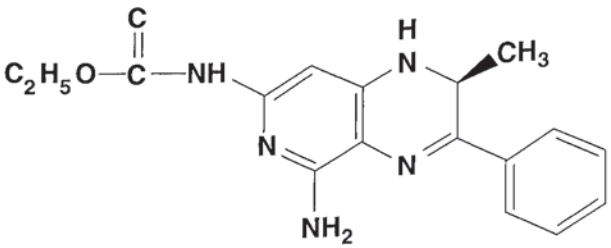

FIG. 1. CI-980 structure.

ducted. In the first, CI-980 was administered to 25 patients as a continuous infusion for 24 hours repeated every 21 days at doses ranging from 1.2 mg/m^2/day to 19.2 mg/m^2/day.[6] The dose-limiting toxicity was reversible CNS toxicity consisting of ataxia or other signs of cerebellar dysfunction, confusion, or disorientation. In the second study, CI-980 was administered intravenously for 3 consecutive days and repeated every 21 days at infusion durations ranging from 1 hour to 24 hours/day.[7–9] On this 3-day schedule, CI-980 was substantially more myelosuppressant when administered as a continuous infusion than when given by shorter infusions. Granulocytopenia was the dose-limiting toxicity for the 72-hour infusion schedule, but CNS toxicity developed in only 1 of 13 patients treated on this schedule.

In phase I evaluations, 3 patients on the 24-hour infusion schedule demonstrated evidence of antitumor activity: a partial response in 1 patient who had advanced colon cancer and metastatic liver disease and a reduction in CA-125 levels in 2 patients who had advanced ovarian cancer. Pharmacokinetic studies showed CI-980 to have an extensive distribution into tissues and high systemic clearance.[7,8]

Based on the lower incidence of CNS toxicity associated with prolonged infusions, the 72-hour schedule of CI-980 at 4.5 mg/m^2/day (13.5 mg/m^2/course) was selected for phase II testing. We report here the results of a phase II trial of CI-980 in patients who had metastatic colorectal carcinoma.

PATIENTS AND METHODS

Patient eligibility criteria included metastatic histologically confirmed and bidimensionally measurable adenocarcinoma of the colon or rectum. Patients could have received one prior regimen for metastatic disease in addition to adjuvant chemotherapy. Patients were required to have a World Health Organization performance status of 0 to 2 and an expected survival duration of longer than 9 weeks. Other study inclusion requirements were adequate hematologic function (absolute granulocyte count [AGC] $\geq$1500/μL, platelet count $\geq$ 100,000/μL); renal function (serum creatinine value $\leq$ 2.0 mg/dL); and hepatic function (total bilirubin $\leq$ 2.0 mg/dL). Prior radiotherapy did not preclude a patient's eligibility, provided that the radiation field had not included the site of measurable disease. Informed consent was required of all patients. Patients could not have known or suspected brain metastases, overt psychosis or mental disability, active congestive heart failure, uncontrolled angina, myocardial infarction in the 6 months before study entry, or hypertension uncontrolled by medication. Standard response and toxicity criteria were used.[10]

Pretreatment evaluation included a complete medical history, physical examination, complete blood count, a multichannel chemistry profile (glucose, BUN, serum creatinine, total protein, albumin, bilirubin, calcium, serum alanine aminotransferase, alkaline phosphatase, sodium, chloride, and potassium); urinalysis; electrocardiogram; chest radiograph; and computed tomography scans to define extent of disease. Complete blood, platelet, and differential counts were obtained weekly, and serum chemistries were repeated at least once every course. If the AGC decreased to <1500/μL, a complete blood count was repeated twice weekly until the count recovered to normal. Computed tomography scans were repeated every two courses, and the electrocardiogram was repeated when the patient discontinued therapy.

Patients were also prospectively monitored by neurologic examinations and neuropsychologic assessment of cognitive functioning. The neuropsychologic battery contained five tests: the Mini-Mental State Examination for a brief global screening of cognitive function to detect serious neurotoxic side effects,[11] the Mattis Dementia Rating Scale as a comprehensive assessment of cognitive functioning,[12] the Hopkins Verbal Learning test for a detailed assessment of learning and memory,[13] the Grooved Pegboard test as an assessment of fine-motor speed and coordination,[14] and the Functional Assessment of Cancer Therapy to assess quality of life.[15] These were performed during screening and repeated on day 4 of each course as close to the end of the infusion as possible. If the procedure done on day 4 detected a clinically significant change, the procedure was repeated daily until functions recovered to normal.

CI-980 was provided in 10-mg vials by Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Co. (Ann Arbor, MI, USA). The drug was reconstituted with 5 mL water for injection (USP), resulting in a concentration of 2 mg/mL. The calculated dose was further diluted in 1000 mL 5% dextrose in water (USP) and administered as a constant rate infusion over 24 hours for 3 consecutive days. Courses were repeated every 21 days.

The starting dose for all patients was 4.5 mg/m^2/day (total dose, 13.5 mg/m^2 over 72 hours). The first course of therapy and the first escalated dose were administered in the hospital to allow careful monitoring of CNS toxicity. If well tolerated, subsequent courses were given on an outpatient basis.

Dose escalations by 0.5 mg/m^2/day above the previous course's dose (CI-980 maximum dose allowed was 5.5 mg/m^2/day or 16.5 mg/m^2/course) were permitted if in the previous course the AGC nadir was >1000/μL, the platelet nadir was >100,000/μL, the maximum grade of nonhematologic toxicity experienced was grade 1 (excluding alopecia, local vein reaction, or grade 2 nausea or vomiting), and no treatment-related CNS adverse events had occurred. The CI-980 dose in the subsequent course was reduced by 1.0 mg/m^2/day if any of the following occurred: AGC nadir <500/μL for 5 days or longer, or AGC nadir <500/μL associated with fever $\geq$ 100.4°F or with a documented infection; platelet count nadir <40,000/μL; clinically significant treatment-re-

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

TABLE 1. *Toxic effects of CI-980 by grade (n = 14 patients)*

Toxic effect	Grade 1	2	3	4
Granulocytopenia	3	3	4	8
Thrombocytopenia	—	1	—	—
Anemia	1	—	—	—
Infection	1	1	—	—
Neutropenic fever	1	—	—	—
Fever of unknown origin	1	5	—	—
Fatigue	8	4	2	—
Lethargy	2	—	—	—
Stomatitis	8	4	—	—
Diarrhea	1	—	—	—
Chills	1	—	—	—
Dizziness	2	—	—	—
Myalgia	—	—	1	—
Proctitis	1	—		
Skin reactions	2	1	—	—
Alopecia	8	4	—	—
Central nervous system effects				
Cortical	14	—	—	—
Sensory	6	—	—	—
Cerebellar	14	—	—	—

lated grade 3 or 4 nonhematologic adverse event; grade 2 CNS toxic effect of cerebellar dysfunction, confusion, or disorientation; or a decrease in the total score of the Mini-Mental State Examination of ≥3 points. The CI-980 dose had to be reduced by 2.0 mg/m^2/day if CNS toxic effects ≥ grade 3 occurred.

RESULTS

Fourteen patients (7 men, 7 women) with a median age of 54 years (range, 40–75 years) were entered on this trial. Tumor response and drug toxicity could be evaluated in all 14. Eight patients had received one prior chemotherapy regimen for metastatic disease. Sites of measurable disease included liver (12 patients) and lung (3 patients). The median number of courses given was two (range, 2–6). A total of 36 courses of CI-980 were given: 23 courses (14 patients) at 4.5 mg/m^2/day; 10 courses (7 patients) at 5.0 mg/m^2/day; and 3 courses (3 patients) at 3.5 mg/m^2/day.

Neither partial nor complete responses were observed. The median time to progression was 7 weeks (range, 6–18 weeks). Three patients experienced stable disease lasting 9, 11, and 15 weeks.

Toxic reactions observed in the 14 study patients are listed in Table 1. Granulocytopenia was common: 8 patients experienced grade 4 granulocytopenia. The median granulocyte nadir, occurring on day 14, was 1700/μL (range, 0–4700/μL), with a median duration of granulocyte suppression of 8.5 days (range, 4–23). Only 1 patient developed neutropenic fever that required admission to the hospital, however. Thrombocytopenia was rare, with only 1 patient developing a grade 2 platelet count during the first course of treatment; this did not recur in the next course at the same dose. Dose reductions were mandatory for grade 4 neutropenia, as previously described. Two patients received granulocyte colony-stimulating factor as treatment for neutropenia. Other non-CNS toxic effects included fatigue, lethargy, infection, fever, skin reactions, alopecia, dizziness, anemia, stomatitis, diarrhea, chills, and myalgia. Cardiotoxicity was not noted in this trial.

Neurologic evaluation and neuropsychologic assessment of cognitive function revealed a significant but reversible decline in recent memory functioning in all patients after each course of CI-980 but with no effect on overall mental status or neurologic function. Neurologic examinations revealed no clinically significant changes other than subjective complaints of memory decline and unsteady gait, typically occurring at the conclusion of the infusion and lasting 2 to 3 days. There were no clinically detected motor or sensory changes on neurologic examination.

Significant effects of CI-980 were detected on the neuropsychologic assessment. Although there was no change in overall cognitive functioning, there was a significant decline in memory performance (both learning and recognition of items presented): 67% of patients performed ≥ 1.5 standard deviations below the normative mean after the first course of treatment. There were also transient, non-significant declines in motor coordination after each course of CI-980, compared with the preinfusion assessment. No changes in quality of life were noted. The details of this neuropsychologic evaluation have been described in a separate report.[16]

DISCUSSION

CI-980 at the dose and schedule studied failed to demonstrate any clinical activity in patients with metastatic colorectal carcinoma. Granulocytopenia was common, yet 50% of the patients were able to receive one dose escalation. The toxic effects observed were consistent with those reported in the phase I trial of the 72-hour schedule, except that all patients in our trial experienced some evidence of mild CNS toxicity.

CI-980 caused a specific, reversible dysfunction of memory, presumably related to its action on cholinergic neurons in the hippocampus.[17] Motor speed and dexterity also declined slightly after each treatment. CI-980 had no effect on overall cognitive functioning or subjective quality of life and did not cause clinically detectable neurologic deficits nor changes in quantitative sensory testing.

At the dose and schedule studied, CI-980 probably did not affect enough cholinergic neurons in the hippocampal region to result in persistent memory loss. Because disease progressed after two courses in most patients and they did not receive CI-980 for multiple courses, the agent's long-term and cumulative neurotoxic side-effects cannot be assessed. The neurotoxic-

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

ity noted with CI-980 is consistent with colchicine's recognized effects on the brain.[18,19]

In another phase II trial of CI-980 administered at the same dose and schedule for advanced epithelial platinum-refractory ovarian carcinoma, only one response was observed in 16 patients.[20,21] Grade 4 neutropenia occurred in 50% of the patients, and CNS toxicity was similar to that reported in our trial.

Preclinical studies of CI-980 did not predict CNS toxicity, and the phase I study of the extended-infusion schedule observed a lower frequency of CNS toxicity. These phase I trials, however, did not use the prospective neuropsychologic testing performed in our trial. Prospective neurologic examinations and neuropsychologic assessment of cognitive functioning in our clinical trial more accurately described CI-980's CNS toxicity profile.

The effects of CI-980 on memory function were reversible and did not appear cumulative. Because of rapid disease progression, however, the study patients did not receive prolonged treatment with CI-980. Thus, its CNS toxicity profile may be more completely defined in patient populations treated for longer durations, and sequential prospective CNS evaluations should be performed. Clinical trials of CI-980 in previously treated soft-tissue sarcoma and recurrent glioma are ongoing.

REFERENCES

1. Cohen AM, Minsky BD, Schilski RL. Colon cancer. In: De Vita VT, Hellman S, Rosenberg SA, eds. *Cancer, principles and practice of oncology*, vol. 1. 4th ed. Philadelphia: J.B. Lippincott 1993:929–77.
2. Conti JA, Kemeny NE, Saltz LB, et al. Irinotecan is an active agent in untreated patients with metastatic colorectal cancer. *J Clin Oncol* 1996;14:709–15.
3. Rothenberg ML, Eckardt JR, Kuhn JG, et al. Phase II trial of irinotecan in patients with progressive or rapidly recurrent colorectal cancer. *J Clin Oncol* 1996;14:1128–35.
4. Wheeler GP, Bowden BJ, Temple C Jr, et al. Biological effects and structure activity relationships of 1,2-dihydropyridol[3,4-6] pyrazines. *Cancer Res* 1983;43:3567–75.
5. Kim SN, Watkins JR, Gough AW. Intravenous toxicity of CI-980, a mitotic inhibitor, in mice and rats [Abstract]. *FASEB J* 5:1991;485.
6. Sklarin NT, Benson L, Roca J, et al. Phase I study of CI-980: 24-hr infusion schedule [Abstract]. *Proc Am Soc Clin Oncol* 1995;14:479.
7. Natale R, Waterhouse D, Grove W, et al. Phase I clinical and pharmacokinetic trial of CI-980, a novel mitotic inhibitor [Abstract]. *Proc Am Soc Clin Oncol* 1992;11:118.
8. Brodfuehrer J, Whitfield LR, Kowal C, et al. Pharmacologically guided dose escalation in phase I clinical trial of CI-980 [Abstract]. *Proc Am Assoc Cancer Res* 1992;33:529.
9. Rowinsky EK, Noe DA, Grochow LB, et al. Phase I and pharmacological study of CI-980, a synthetic and structurally unique antimicrotubule agent, on a 72-hour continuous infusion schedule in adults with solid tumors [Abstract]. *Proc Am Soc Clin Oncol* 1995;14:459.
10. Ajani JA, Welch SR, Raber MN, et al. Comprehensive criteria for assessing therapy-induced toxicity. *Cancer Invest* 1990;8:147–59.
11. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of outpatients for the clinician. *J Psychiatr Res* 1975;12:189–98.
12. Mattis S. Dementia Rating Scale. Odessa, FL: Psychological Assessment Resources, Inc., 1988.
13. Brandt J. The Hopkins Verbal Learning Test: development of a new memory test with six equivalent forms. *Clin Neuropsychol* 1991;5:125–42.
14. Mathews CG, Kløve H. Instruction manual for the adult neuropsychological test battery. Madison, WI: University of Wisconsin Medical School, 1964.
15. Cella DF, Tulsky DS, Gray G, et al. The functional assessment of cancer therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;11:570–9.
16. Meyers CA, Kudelka AP, Conrad CA, et al. Neurotoxicity of CI-980, a novel mitotic inhibitor. *Clin Cancer Res* 1997;3:419–22.
17. Peterson GM, McGinty IF. Direct neurotoxic effects of colchicine on cholinergic neurons in medial septum and striatum [Letter]. *Neuroscience* 1988;94:46–51.
18. Di Patre PL, Oh JD, Simmons JM et al. Intrafimbrial colchicine produces transient impairment of radial-arm maze performance correlated with morphologic abnormalities of septohippocampal neurons expressing cholinergic markers and nerve growth factor receptor. *Brain Res* 1990;523:316–20.
19. Mundy WR, Tilson HA. Neurotoxic effects of colchicine. *Neurotoxicology* 1990;1:539–47.
20. Verschraegen CF, Kudelka AP, Edwards CL, et al. Phase II trial of CI-980 in advanced epithelial ovarian carcinoma [Abstract]. *Proc Am Soc Clin Oncol* 1995;14:271.
21. Verschraegen CF, Kudelka AP, Edwards CL, et al. Update of a phase II trial of CI-980 in advanced epithelial ovarian carcinoma [Abstract]. *Proc Am Soc Clin Oncol* 1997;16:30a.

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.