

## Neurotoxicity of CI-980, a Novel Mitotic Inhibitor

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### ABSTRACT

CI-980 is a chemotherapeutic agent currently in Phase II trials that arrests cellular division by binding to tubulin. It is structurally and functionally similar to colchicine, a potent nonreversible neurotoxin, and is able to cross the blood-brain barrier. In Phase I studies, neurotoxicity was noted. The neurotoxicity of CI-980 was prospectively evaluated in two Phase II studies by neurological evaluation, quantitative sensory testing, and neuropsychological assessment of cognitive functioning. The results revealed a significant but reversible decline in recent memory functioning after each course of CI-980, with no effect on overall mental status or neurological function. Sixty-seven percent of patients performed in the impaired range on the memory test after their first infusion, whereas only one exhibited a decline on a brief cognitive screen. The results are consistent with the known effects of colchicine on the brain. Colchicine selectively blocks choline acetyltransferase in the hippocampus and basal forebrain, the area of the brain responsible for memory consolidation. Although the effect of CI-980 was reversible at the dose and schedule used, this study suggests that careful monitoring of cognitive function in patients receiving this agent should be performed if dose or schedule parameters are changed. In addition, this study demonstrates the feasibility of incorporating neuropsychological assessment in clinical trials of new anticancer agents having potential neurotoxic side effects.

### INTRODUCTION

CI-980 is a synthetic mitotic inhibitor that binds to tubulin at the colchicine binding site, inhibiting the polymerization of microtubules and arresting cellular division in metaphase (1). It shares structural and functional similarities with colchicine

(Fig. 1), but unlike colchicine, it crosses the blood-brain barrier. Colchicine is a potent neurotoxin used by neuroscientists to study brain-behavior relationships. Colchicine selectively damages cholinergic neurons within the hippocampus and basal forebrain without damaging other adjacent neurons (2-4). The hippocampus is a critical structure for the storage of new learning and memory (5). The neurotoxicity of colchicine is dose-dependent, with relatively selective damage seen at smaller doses and less selective, larger areas of damage observed after larger doses. In addition, the damage observed is progressive and persistent (6, 7). Colchicine is also reported to cause epileptiform activity and seizures as a result of neuronal injury to the hippocampus (3). How colchicine's effect on tubulin leads to such selective damage to cholinergic hippocampal neurons is unknown. One possible explanation is the heterogeneity of microtubules; there are over 20 different isomers of tubulin in the brain that may be differentially sensitive to a given concentration of colchicine (8).

Phase I experience with CI-980 revealed severe dose-limiting neurological side effects, including confusion, lethargy, dizziness, incoordination, delirium, ataxia, and coma (9, 10). Interestingly, the preclinical animal studies did not reveal clinical signs of neurotoxicity at i.v. lethal doses (11). Thus, the present study was conducted to closely monitor central nervous system function in patients receiving CI-980.

### PATIENTS AND METHODS

Individuals with ovarian and colorectal cancer were enrolled in this Phase II protocol. The demographic characteristics of the patients are listed in Table 1. The ovarian and colorectal patients were comparable in terms of age (mean 56.4 versus 57.0 years, respectively) and education (mean 14.5 versus 13.2 years, respectively). The ovarian cancer patients had failed platinum-based front-line chemotherapy, whereas the colorectal patients had no previous systemic chemotherapy for metastatic disease. Patients with central nervous system involvement of cancer or concurrent neurological or psychiatric illness were excluded from the study. Twenty-nine patients were seen at baseline, before starting CI-980 treatment. There was attrition over time due to disease progression. Twenty-three patients were evaluated before beginning a third course of treatment, but only eight of these were eligible for continued therapy and were seen after the third course. Patients were monitored by neurological examinations, quantitative fine sensory testing, and a battery of neuropsychological tests before and after each course of therapy. Fine sensory testing was performed by temperature and vibration threshold analysis using Physitemp instrumentation (Physitemp Instruments, Clifton, NJ). Threshold discrimination values obtained were compared to previously established normal values at this institution. All the neurological examinations were performed by a single neurologist (C. A. C.) for uniformity.

The neuropsychological battery contained the following

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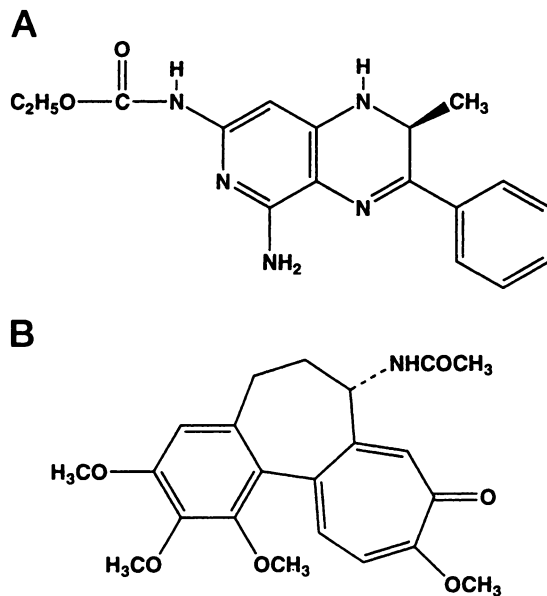


Fig. 1 A, chemical structure of CI-980. B, chemical structure of colchicine.

five tests: (a) the MMSE<sup>2</sup> was used as a brief global screening of cognitive function to detect and follow any serious neurotoxic side effects (*i.e.* delirium; Ref. 12). The total score possible is 30; the usual cutoff score for dementia is 24, and a 3-point drop is considered indicative of neurotoxicity; (b) the Mattis DRS was used as a more comprehensive assessment of cognitive functioning (13). The total score is 144; normal subjects rarely score below 137. The subtests of this scale measure attentional abilities (37 points), frontal lobe executive functioning (37 points), visual-construction (6 points), abstract reasoning (39 points), and immediate memory and orientation (25 points); (c) the Hopkins Verbal Learning Test was administered as a more detailed assessment of learning and memory, especially because administration of CI-980 was hypothesized to alter hippocampal function (14). This scale measures the ability to learn a list of 12 semantically related words over 3 trials and to recognize the words just rehearsed. This test has six alternate forms, making it suitable for repeated assessments. The total number of words recalled over three trials is calculated; scores  $\leq 21$  are considered impaired. The ability to accurately recognize  $\leq 10$  of 12 words is also considered impaired; (d) the grooved pegboard test was used as an assessment of fine motor speed and coordination (15). This test requires the person to insert pegs into a board as rapidly as possible. Average performance time on this test is approximately 70 s; and (e) the FACT was administered as an assessment of quality of life (16). The scale has a total possible score of 132. The average score in a group of cancer patients is 82, with a SD of 16. Scores on the cognitive tests are expected to remain stable or improve (due to the effects of repeated

<sup>2</sup> The abbreviations used are: MMSE, mini-mental state; DRS, dementia rating scale; FACT, functional assessment of cancer therapy.

Table 1 Patient characteristics (N = 29)

	No. of patients	Mean (range)
Cancer diagnosis		
Ovarian	15	
Colorectal	14	
Sex		
Males	7	
Females	22	
Age (yrs)		56.7 (35–75)
Education (yrs)		13.9 (7–20)

administration) on the postbaseline assessments if no change in the patient's clinical status occurs. *t* tests for paired samples were used to compare the results of the different test administrations, and *t* tests for independent samples were used to compare the results obtained for the ovarian and colorectal groups.

CI-980 was administered as 3 consecutive 24-h infusions of 4.5 mg/m<sup>2</sup>/day, in effect giving a 72-h continuous infusion. Courses were repeated every 21 days. If the drug was very well tolerated, the dose at the next course was increased by 0.5 mg/m<sup>2</sup>/day; the dose was decreased if toxic effects occurred.

## RESULTS

The efficacy of CI-980 in ovarian and colorectal cancer is described elsewhere (17, 18). One patient developed hallucinations and a prolonged delirium during her first 24-h infusion, which was thought to be related to hyponatremia and cleared promptly with sodium correction. The neurological examinations in the remaining patients revealed no clinically significant changes other than subjective complaints of memory decline and unsteady gait. These symptoms typically occurred at the end of the 3rd day of infusion and lasted for 2–3 days. Axial and appendicular cerebellar testing did not change significantly. There were no clinically detected motor or sensory changes on neurological examination related to CI-980 therapy.

Thirteen ovarian cancer patients received serial fine sensory evaluations. Twelve patients had abnormal vibratory thresholds, of which 10 had been abnormal at the time they entered the study. Three patients had worsening vibratory discrimination thresholds. However, thresholds in four patients actually improved during the treatment course. Only two patients had an isolated abnormal temperature discrimination threshold, and both improved with additional treatment courses. Thus, quantitative sensory evaluation did not reveal any pattern referable to CI-980 treatment. The findings obtained were likely related to prior therapy that affected peripheral nerve function that was resolving off treatment.

In contrast to results of the neurological and quantitative sensory testing, significant effects of CI-980 were detected on the neuropsychological assessment. Table 2 lists the test scores before and after each course of therapy over three courses. There was no change in overall cognitive functioning as assessed by the MMSE and the DRS over the course of the study. Interestingly, scores on the DRS actually improved over time as a result of practice effects, demonstrating the limited usefulness of tests without alternate forms in clinical trials. However, there was a significant drop in memory performance (both learning and

Table 2 Neuropsychological test results (mean scores)<sup>a</sup>

Test	N =	1st course		2nd course		3rd course	
		Pre (29)	Post (27)	Pre (27)	Post (27)	Pre (23)	Post (8)
MMSE		27.6	27.3	27.6	27.9	27.5	27.6
DRS							
Total		137.5	138.1	139.3	139.4	139.7	139.4
Attention		36.1	35.9	36.2	36.0	36.3	36.4
Initiation		36.0	36.0	35.9	36.4	36.4	35.1
Construction		5.9	5.8	6.0	5.7	6.0	5.6
Conceptualization		36.1	36.5	37.5	37.6	37.7	38.3
Memory		23.3	23.8	23.8	23.7	23.4	24.0
Hopkins Verbal Learning							
Total recall		22.6	18.4 <sup>b</sup>	22.1	20.6 <sup>b</sup>	24.7	19.5 <sup>b</sup>
Recognition		10.6	9.5 <sup>b</sup>	11.4	10.0 <sup>c</sup>	10.9	10.5
Grooved pegboard							
Dominant hand		80.8	87.7	75.2	76.6	72.9	84.3
FACT		84.4	-	84.9	-	84.4	-

<sup>a</sup> Pre, pretreatment; post, posttreatment. *N* values are shown in parentheses under each of these subheadings.

<sup>b</sup> Difference between baseline and follow-up score significantly different at  $P < 0.01$ .

<sup>c</sup> Difference significant at  $P < 0.05$ .

recognition of items presented) on the Hopkins Verbal Learning Test after each course of therapy that recovered before the next course was administered. In fact, 67% of patients performed  $\geq 1.5$  SDs below the normative mean after the first course of treatment (only 6.7% of the normal population would be expected to score in this range). Fig. 2 displays the disparity between memory and global cognitive functioning over time. The memory subsections of the DRS and the MMSE did not change, however. These tests measure orientation and immediate memory, as opposed to learning new information. The ability to learn and retain new information is a function subserved by the hippocampus, whereas immediate memory (as assessed by the MMSE and the DRS) is more a function of intact attentional abilities and is generally not impaired except in cases of encephalopathy or dementia.

Preexisting cognitive deficits did not seem to place patients at greater risk for declines in memory functioning. Eight patients scored in the impaired range on the DRS at baseline (DRS score  $< 136$ ). These patients declined an average of 3 points on the Hopkins Verbal Learning Test after the first infusion (mean score at baseline = 17.5; mean score after infusion = 14.5), whereas the group of patients scoring at least 136 points on the DRS at baseline exhibited a 4.5-point decline on the memory test after the infusion (mean score at baseline = 24.5; mean score after infusion = 20.0). However, there was an excessive decline in motor coordination after CI-980 infusion in the cognitively impaired group compared to the intact group (1.10 versus 0.06 SD decline, respectively, on the grooved pegboard test, dominant hand). There was no difference between the impaired and unimpaired groups on the amount of change on the other tests after CI-980 treatment.

There was no difference between the ovarian and colorectal cancer patient groups on any of the neuropsychological tests at baseline, but the groups differed on the Hopkins Verbal Learning Test after the first course of therapy. Patients with ovarian cancer performed better on the recall portion of this test (mean

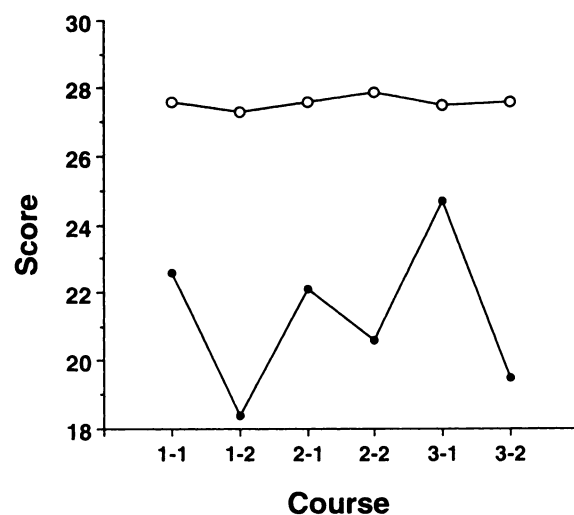


Fig. 2 Graph of the mean memory recall scores from the Hopkins Verbal Learning Test (●) and the score on the MMSE (○) before and after each course of therapy. *X* axis (time points): first number, the course of treatment (1, 2, or 3); second number, the pretreatment assessment (1) or posttreatment assessment (2).

20.1 versus 16.6;  $P < 0.05$ ), suggesting that the colorectal patients may have experienced more severe effects of CI-980 on hippocampal function after the first course of therapy. The groups did not differ in their subsequent performance on this measure. Patients with colorectal cancer had significantly better quality of life scores on the FACT at baseline (91.9 versus 77.8;  $P < 0.01$ ), but quality of life did not differ significantly between the two groups during treatment (*i.e.* the FACT scores of the ovarian group increased slightly, and they decreased slightly in the colorectal group).

## DISCUSSION

The results of this study show that CI-980 caused a specific, reversible dysfunction of memory, consistent with our hypothesis that the toxicity of CI-980 would be similar to that seen with colchicine. Motor speed and dexterity also declined slightly after each course of treatment in patients with prior cognitive impairment. In contrast, CI-980 had no effect on overall cognitive functioning or subjective quality of life. Patients with pretreatment impairments on these cognitive tests were at no greater risk for experiencing neurotoxic side effects. The magnitude of memory decline was similar in patients with and without baseline cognitive impairment. In addition, the appearance of side effects was not related to patient diagnosis, age, or prior systemic cancer treatment. CI-980 did not cause clinically detectable neurological deficits or changes in quantitative sensory testing. The number of patients who showed improvement of large-fiber fine-sensory (vibratory) discrimination was equal to the number of patients who worsened. Additionally, small-fiber sensory (temperature) discrimination did not significantly change over the course of treatment.

The similarity between CI-980 and colchicine toxicity on memory function suggests an effect on the cholinergic neurons in the hippocampus. At the dose and schedule studied, CI-980 likely did not affect enough neurons to cause persistent memory loss in these patients. It must be noted, however, that this study may underestimate the long-term neurotoxic side effects of CI-980 because patients were withdrawn from the study early due to progressive disease (from  $n = 29$  at baseline to  $n = 8$  after the third course of therapy). CI-980 has been found to have potential anticancer activity in ovarian cancer (18)<sup>3</sup> and is undergoing clinical trials in other tumor types.

Agents that disrupt tubulin function have an array of potential effects on the central nervous system. For instance, microtubule disruption has been proposed as an etiology in several neurodegenerative diseases. Endogenous colchicine-like substances have been hypothesized to underlie the development of Alzheimer's disease (19). Colchicine and mescaline have structural homology, and a disruption of the cytoskeleton has been proposed to have an etiological role in the action of hallucinogens and the development of schizophrenia (20). Given the plethora of anticancer agents that bind to tubulin as their mechanism of action, careful monitoring of nervous system function, both peripheral and central, may lead to a better understanding of the long-term effects of these agents. This is particularly important because patients are living longer because of the efficacy of these therapies. Careful documentation of neurotoxic side effects may lead to less toxic but equally efficacious dose and scheduling of these agents and may allow for the institution of interventions in patients who do experience impairments of their memory or other cognitive functions.

<sup>3</sup> Unpublished data.

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