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Phase II study of CI-958 in colorectal cancer

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Abstract *Purpose*: We completed a phase II trial of CI-958 (NSC 635371) in patients with advanced colorectal cancer given at a dose of 700 mg/m^2 every 21 days. *Methods*: All 15 patients had metastatic disease and had been previously treated with one 5-fluorouracil-based regimen in an adjuvant (six) or metastatic (nine) setting. *Results*: None of the patients treated with CI-958 had an objective response to treatment. Median survival was 4.8 months after the start of treatment. Leukopenia was the major toxicity, but no patient experienced febrile neutropenia. An acute febrile reaction was seen after infusion in four of the first nine patients treated. This was abrogated by pretreatment with dexamethasone in the remaining patients. *Conclusions*: CI-958 was not effective at this dose and schedule in patients with previously treated advanced colorectal cancer.

Key words CI-958 · Colon · Rectal · Phase II

Introduction

Colorectal carcinoma continues to be the second most common cause of cancer death in America with an estimated 56 500 deaths in 1998 [5]. While 5-fluorouracil (5-FU) remains the "standard therapy" of metastatic disease its response rate is only in the range of 10–40% [1]. Numerous attempts have been made to increase the efficacy of 5-FU by employing altered schedules and the addition of response modifiers such as leucovorin, but these have had little impact on survival [6]. Irinotecan is the other approved drug for the treatment of colorectal cancer in 5-FU failures, and its response rate is a modest 13% [8]. Therefore, new chemotherapy agents are needed for this deadly disease. We evaluated CI-958 for use in patients with advanced colon cancer refractory to 5-FU. We employed CI-958 700 mg/m^2 every 21 days based on the results of a previous phase I trial [2].

CI-958 [5-[(2-aminomethyl)amino]-2-[2-(diethylamino)ethyl]-2H-[*l*]benzothiopyrano[4,3,2-*cd*]-indazol-8-ol trihydrochloride, (NSC #635371)] is a synthetic intercalating agent with cytotoxic activity against mammalian cells in culture and with antitumor activity against transplanted tumors in mice. CI-958 is a representative of a new chemical class, the benzothiopyranoindazoles [4, 9]. Chemically, this novel series is most closely related to the thioxanthenones. Thioxanthenone drugs have been used as antiparasitic agents (e.g. hycanthone, lucanthone), but these compounds have only marginal anticancer activity. CI-958 resembles another synthetic DNA intercalator, mitoxantrone, in having two basic side-chains attached to a planar ring system.

CI-958 is a moderately potent DNA binder, and its intercalating activity is demonstrated by its ability to unwind closed circular DNA. Like doxorubicin and mitoxantrone, but unlike the anthrapyrazoles, CI-958 inhibits the synthesis of DNA and RNA about equally. It produces protein-associated single- and double-strand breaks in DNA. This pattern of breaks strongly suggests that CI-958 acts by stabilizing the cleavable complex of DNA with topoisomerase II, though direct evidence for this has not been obtained. Like doxorubicin, CI-958 produces breaks that are repaired very slowly. CI-958 exhibits broad-spectrum activity against transplanted murine tumors and human tumor xenografts. In a panel of 14 solid tumor systems, including some very refractory systems, CI-958 displayed significant activity in 14, and high-level activity in 9 (investigators brochure). Based on this encouraging preclinical activity, we

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studied CI-958 as part of a phase II trial in patients with advanced colorectal cancer.

Materials and methods

Patients with histologic evidence of colorectal adenocarcinoma were eligible for the trial. The tumor could be locally recurrent or metastatic, but had to be measurable. Patients could be chemotherapy naive or may have received one prior 5-FU-containing regimen. The 5-FU-containing regimen had to have been given either as adjuvant treatment or for metastatic disease, but not both. Eligible patients had to have a life expectancy over 8 weeks and a (Zubrod's) performance status ≤ 2. Patients had to have adequate bone marrow function, defined as a peripheral absolute granulocyte count of $> 2000/mm^3$ and platelet count of $> 100\,000/mm^3$; adequate liver function (bilirubin of ≤ 1.5 mg%); and adequate renal function (creatinine of < 1.5 mg%). Patients were 18 years of age or over and could not have known brain metastases. Patients could not have received any chemotherapy in the 4 weeks prior to trial entry and must have recovered fully from the toxic effects of that therapy. Patients had to give their written informed consent for this investigation, which was approved by the Institutional Review Board.

CI-958 700 mg/m^2 was given by a 2-h infusion via a central venous access device. Treatment was to be given every 21 days in the absence of progressive disease or prohibitive toxicity. The dose was reduced to 560 mg/m^2 for nadir granulocyte counts below $1000/mm^3$, platelet counts below $75\,000/mm^3$, or other grade 3 toxicity. The drug was to be discontinued for grade 4 toxicity, except for marrow toxicity and its sequelae such as infection or bleeding. The drug was supplied by the National Cancer Institute, Division of Cancer Treatment (Bethesda, Md).

A two-stage design was used to minimize the expected number of colorectal cancer patients who were treated with CI-958, in the event that it proved to be very disappointing [3]. This phase II study design permitted early termination of patient entry after the first 15 response-evaluable patients if no complete or partial responses were seen. Response and progressive disease were defined by the usual criteria [7]. Patients could be removed from study because of disease progression, toxicity, or patient request. Repeat tumor measurements were to be obtained every two courses of therapy. A minimum of two courses was required for a patient to be considered as having received an adequate trial to evaluate efficacy. If there was clear progression of disease after one course of treatment, however, the patient was considered a treatment failure. All patients were to be evaluated for toxicity using the NCI scale.

Results

The trial was opened for accrual in May 1996 and the last patient enrolled in August 1996. A total of 15 patients were enrolled and all were evaluable for treatment response and toxicity. The patient characteristics included 10 males and 5 females, ranging in age from 35 to 75 years (Table 1). Of the 15 patients, 12 had colon cancer and 3 had rectal cancer. One patient had recurrence limited to the peritoneum, the rest had liver involvement (14) in addition to lung (6), retroperitoneal (2), or bladder involvement (1). All patients had had previous therapy with a 5-FU-based regimen, with six having received adjuvant treatment and recurring 5–29 months after initial diagnosis. Of the nine who had received previous treatment for advanced disease, five were found to have advanced disease at diagnosis, and four had recurred between 7 and 25 months after initial surgery. All but one patient had a baseline performance status of 0 or 1.

Table 1 Patient characteristics

Gender	
Male	10
Female	5
Age (years)	
Median	60
Range	35–75
Racial group	
Caucasian	10
African-American	5
Primary site	
Colon	12
Rectum	3
Metastatic sites	
Liver	14
Lung	6
Retroperitoneum	2
Performance status (Zubrod)	
0	6
1	8
2	1

Response

No patient had an objective response to therapy. One patient developed progressive intraperitoneal disease after one cycle of therapy and was removed from the trial. Ten patients progressed after two cycles, three patients received four cycles, and one patient six cycles. Of the four patients receiving more than two cycles, only one had even a minor response (8% decrease in size) after two cycles, but died of liver failure just after receiving the fourth cycle. Survival from entry on the study ranged from 1.7 to over 14 months (median 4.8).

Toxicity

The major toxicity was marrow suppression as manifested by leukopenia (Table 2). Nine patients developed grade 3 or 4 neutropenia, although no patient experienced febrile neutropenia. Four patients had dose adjustments made in subsequent cycles for neutropenia. No patient had a platelet count of less than $100\,000/mm^3$ during therapy.

Table 2 Numbers of patients and the worst hematologic toxicity ($n = 15$)

	Grade			
	0–1	2	3	4
Leukopenia	3	4	7	1
Neutropenia	3	3	8	1
Thrombocytopenia	15	0	0	0

Four of the first nine patients developed a fever within 8 h of the first infusion of the CI-958. In all but one of these patients the fever resolved by the next day. That patient developed a fever as high at 105°F, and she was kept in the hospital for 4 days. All cultures were negative. After this experience with fever, the last six patients treated on protocol received premedication with dexamethasone 10 mg i.v. in addition to regular antiemetics and none developed fever associated with drug administration.

Only four patients were hospitalized after treatment. One patient developed bowel obstruction after the first cycle, and was judged to have progressive disease when extensive abdominal disease was found at laparotomy. One patient developed gram-negative bacteremia 1 week after the first dose of drug. He had an ileal conduit after bladder resection for tumor involvement, and had had a previous infection with the same organism. His white blood count was normal at the time of admission. The third patient was hospitalized with fluid retention after his second cycle of treatment. His baseline creatinine was 1.1 mg/dl and was 1.5 mg/dl at the time of the second treatment. He was hospitalized 3 weeks later with fluid retention and his creatinine reached 2.2 mg/dl. He was removed from the protocol because of failure to respond and this complication. The fourth patient had slight regression of his extensive liver tumor after the second cycle, but was then hospitalized with-poglycemia (glucose 49 mg/dl) after the third cycle. Two days after his fourth cycle of therapy he was admitted to the hospital obtunded with a glucose less than 20 mg/dl, elevated ammonia and BUN and then died. The death was thought to be secondary to progressive liver disease.

Discussion

Unfortunately, CI-958 was not found to be active in our study of patients with advanced colorectal cancer. None of the 15 patients achieved an objective partial response, and 11 patients received only two cycles or fewer because of rapid disease progression. This poor response rate may have been in part due to the patient population under study. All patients had been previously treated with a 5-FU-based regimen, with nine having failed treatment for advanced disease and six recurring after adjuvant treatment. While the protocol was open to chemotherapy-naive patients, all patients had been previously treated because of referral patterns and ready availability of 5-FU on and off protocol. Given the generally poor response to 5-FU we considered that it was reasonable to treat patients with new agents as part of first-line therapy. Most of the patients were of good performance status, with only one patient being grade 2. In a previous phase II trial CI-958 has been shown to be of use in the treatment of hormone-refractory prostate cancer [10].

The toxicity of the drug was tolerable, with myelosuppression being dose limiting as expected from phase I and II trials [2, 10]. At the dose employed, even though there was significant grade 3 neutropenia, only one patient had grade 4 neutropenia, and no patients developed febrile neutropenia. One patient died with hepatic failure 2 days after receiving his fourth course of treatment. It was thought that this was more likely related to progressive disease than the drug. Another patient developed an elevated creatinine and fluid retention, that was thought to possibly be related to the CI-958. The most common toxicity was the development of fever shortly after the first infusion of the drug. It developed in four out the first nine patients. After this initial experience we routinely gave dexamethasone to the patients as a premedication, in addition to antiemetics, and no further fevers were seen. This side effect had previously been seen in three patients treated on a phase I trial, but was not thought to be from the drug (investigator's brochure). Fever and chills have been reported in a phase II trial for prostate cancer [10]. Our results suggest that this association should be further explored in future trials.

In summary, while CI-958 was well tolerated in this trial, it did not produce any objective responses in this group of patients with advanced colorectal cancer refractory to 5-FU. Future trials may consider using CI-958 as the initial treatment of patients, to help avoid resistance, or with a different schedule.

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