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Clinical trial report

Phase II trial of echinomycin in patients with advanced or recurrent colorectal cancer

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Abstract. Echinomycin is a novel bifunctional intercalating agent derived from *Streptomyces echinatus*. A phase II clinical trial of echinomycin in patients with advanced, measurable colorectal cancer was initiated to determine the efficacy and toxicities of this agent. Echinomycin, 1.5 mg/m^2, was given initially as a 30- to 60-min infusion every 4 weeks. After 4 episodes of anaphylaxis had occurred among the first 14 patients, the schedule was changed to a 24-h infusion, and an additional 16 patients were treated on this schedule. Treatment was given every 3 weeks. A total of 30 patients were eligible and evaluable; there were 3 (10%; 90% confidence interval, 3%–23%) clinical responses lasting 3, 3+, and 12 months, respectively. The most serious toxicity encountered was anaphylaxis, which occurred in 5 patients, although with no serious sequelae. A premedication regimen with dexamethasone, diphenhydramine, and cimetidine and a change in the duration of the infusion to 24 h reduced the incidence of this complication. Grade 2–3 vomiting occurred among earlier patients treated; however, with the 24-h schedule this toxicity was substantially reduced. The sole important case of hematologic toxicity was a single patient with grade 3 thrombocytopenia. Echinomycin employed in this dose and schedule had modest activity against colorectal cancer, comparable with that observed with 5-fluorouracil. Further studies in patients with gastrointestinal malignancies using a 24-h infusion with a dexamethasone premedication regimen similar to that employed prior to administration of taxol may be warranted.

Key words: Echinomycin – Colorectal cancer – Phase II

Introduction

Strategies in the treatment of advanced colorectal cancer have largely focused on modulation of fluoropyrimidine activity by agents such as leucovorin, interferon, and *N*-(phosphonacetyl)-*L*-aspartate (PALA). While preclinical evidence for the efficacy of these regimens is strong, the results of a recent large trial from the Southwest Oncology Group demonstrated parity for modulated fluorouracil (5FU) regimens with conventionally administration of 5FU in patients with advanced colorectal cancer [1]. These results suggest that new agents with activity in colorectal cancer may be a potentially useful alternative to treatment with 5FU-based regimens.

Echinomycin (quinomycin A, NSC 526417) is a novel quinoxaline antibiotic originally isolated from *Streptomyces echinatus* that has antiviral and antitumor activity [2–4]. Echinomycin consists of two planar quinoxaline moieties connected by an octapeptide bridge [5]. The planar structure allows intercalation into DNA with simultaneous binding to both DNA strands with a 4-bp binding site [6]. Echinomycin was the first bifunctional intercalating agent identified. In an in vitro model employing *Bacillus megaterium*, echinomycin inhibited RNA synthesis with 4–5 times higher potency than actinomycin D and halted DNA synthetic activity within 60 s [7]. In antitumor screening, echinomycin demonstrated activity against two implanted murine tumors, P388 and B16 melanoma [8]. In the human tumor stem-cell assay, echinomycin was active against breast cancer (24%), sarcoma (38%), and colorectal cancer (25%) [9]. Four phase I trials were conducted using different schedules of echinomycin that demonstrated the tolerability of this agent. Thus, echinomycin is a conceptually interesting agent with a novel mechanism of action to explore against solid tumors.

Patients and methods

Eligibility. Patients were required to have histologically proven adenocarcinoma of the colon or rectum beyond the scope of surgical re-

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Table 1. Demographic characteristics

	Patients (*n*)
Entered	30
Eligible	30
Age (years):	
Range	32–82
Median	66
M:F	19:11
Primary site:	
Colon	17
Rectum	13
Performance status:	
0	10
1	20
Sites of metastasis:	
Liver	15
Lung	9
Pelvis	8
Lymph nodes	4
Bone	3
Peritoneum	3
Subcutaneous	1
Number of sites of metastatic disease:	
1	16
2	12
>2	2

section. All patients had measurable disease and had received no prior chemotherapy. Patients were required to be fully ambulatory with adequate nutritional intake, recovery from surgery, and life expectancy. All patients had adequate bone marrow function (leukocyte count, ≥4000 cells/mm^3; platelet count, ≥100,000 cells/mm^3; hemoglobin value, ≥10 g/dl), renal function (creatinine level, ≤1.5 mg/dl; blood urea nitrogen value, ≤25 mg/dl), and hepatic function (bilirubin level, ≤1.5 mg/dl). All patients gave informed consent.

Study design. This study was initiated at the Albert Einstein Cancer Center to determine the objective response rate and clinical toxicities of echinomycin in patients with advanced colorectal cancer. Echinomycin was given initially at 1.5 g/m^2 over 30–60 min every 4 weeks. After 4/14 patients had experienced anaphylactic reactions, the protocol was amended to administration of echinomycin to subsequent patients over 24 h preceded by premedication with dexamethasone, diphenhydramine, and cimetidine. In the absence of any significant hematologic toxicity on the every-4-week schedule, patients receiving echinomycin over 24 h also received treatment every 3 weeks. An additional 16 patients were treated on this schedule. The National Cancer Institute Common Toxicity Criteria [10] were employed to assess toxicity and the Eastern Cooperative Oncology Group (ECOG) standard criteria to assess response [11]. Doses were withheld for renal or hepatic toxicity. Patients who experienced an anaphylactic reaction or other severe toxicity were removed from study. Patients were also removed from study for progressive disease. The study employed a two-stage sampling design with probabilities of >91% of accepting the drug and <7% of rejecting the drug if the true activity was 20% [12].

Results

Demographic characteristics

As shown in Table 1, 30 patients were enrolled in this clinical trial. All were eligible and fully evaluable. All patients had metastatic or locally recurrent disease, were ambulatory, and had received no prior chemotherapy. All other characteristics were typical of the patient population seen at the Albert Einstein Cancer Center, except that the median age of the patients was approximately 5 years higher than that observed in our previous studies.

Table 2. Toxicities[a]

	ECOG grade			
	1	2	3	4
Neutropenia	0	0	0	0
Thrombocytopenia	2	0	1	0
Anemia	1	1	1	0
Hemorrhage	0	0	0	0
Infection	0	0	0	0
Emesis	5	13	5	0
Diarrhea	2	0	0	0
Stomatitis	0	0	0	0
Hepatic	2	3	3	1
Renal	2	0	1	0
Cardiac	0	0	0	0
Neurologic	0	1	1	0
Skin	3	1	1	0

[a] Number of patients with toxicity (n = 30)

Toxicities

The most clinically significant toxicity observed in this clinical trial was anaphylaxis. Five patients experienced this toxicity, four during the first course and one during the second course. These were generally mild reactions characterized by flushing and/or mild wheezing, but they required hospital admission for observation and removal from study in all cases. After 4/14 patients treated with a 15-min infusion had experienced an anaphylactic episode, the infusion duration was increased to 24 h and the premedication regimen now commonly used prior to administration of taxol was employed. Among 16 subsequent patients treated in this fashion, only 1 required removal from study for anaphylaxis.

Other toxicities encountered are shown in Table 2. Emesis was problematic; however, with the introduction of the 24-h infusional schedule, this problem was ameliorated among later patients. An asymptomatic rise in transaminases or serum bilirubin was observed in eight patients. These increases resolved spontaneously. One additional patient had a 10-fold rise in transaminases and serum bilirubin accompanied by renal insufficiency. Both the renal and the hepatic toxicity resolved over a 2-month period with no further sequelae. One patient experienced a nonfatal cerebrovascular accident 1 week after treatment with echinomycin. One patient developed grade 3 erythema and moist desquamation at the site of drug administration, which resolved spontaneously, and irritation at the peripheral infusion site was observed in two other patients. Subsequent patients were treated via a central venous catheter. There was no significant leukopenia associated with administration of this drug.

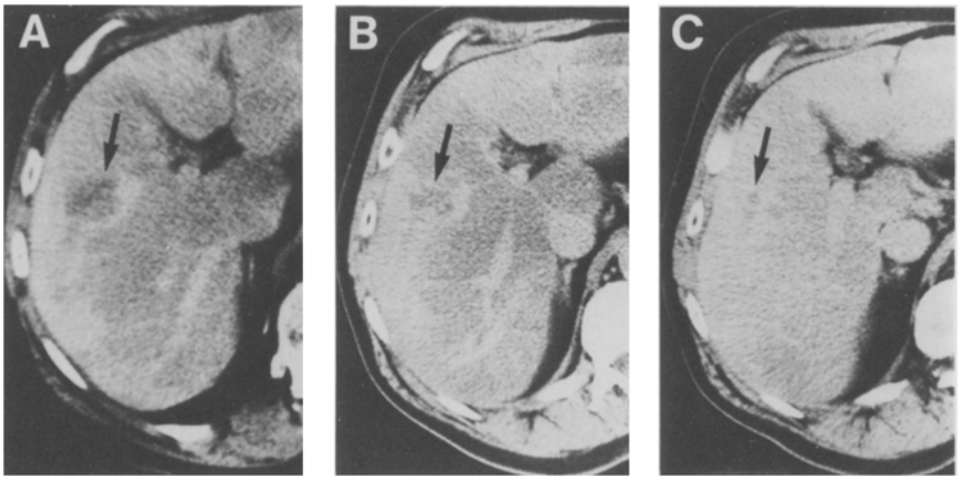

Fig. 1. A–C. Computed tomograpic scans of a lesion in the right lobe of the liver of patient 9. A 3- × 3-cm lesion (*arrow*) regressed over a 2-month period of treatment with echinomycin. The patient remained in response for 12 months

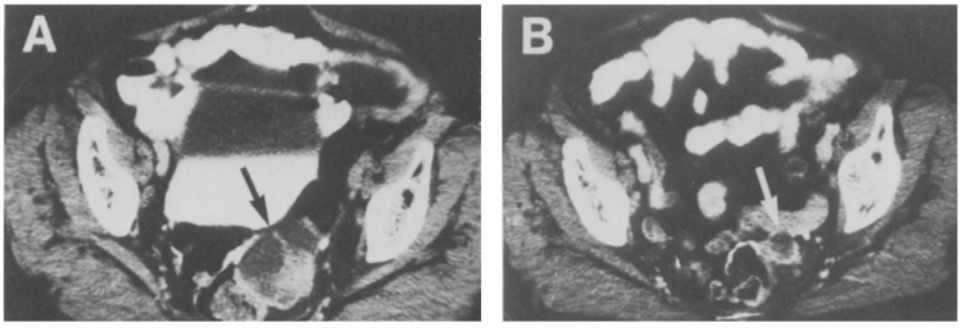

Fig. 2. A, B. Computed tomographic scans of the pelvis of patient 23, demonstrating regression of a 5- × 6-cm pelvic lesion (*arrow*) at 2 months. The patient remained in response for an additional 3 months

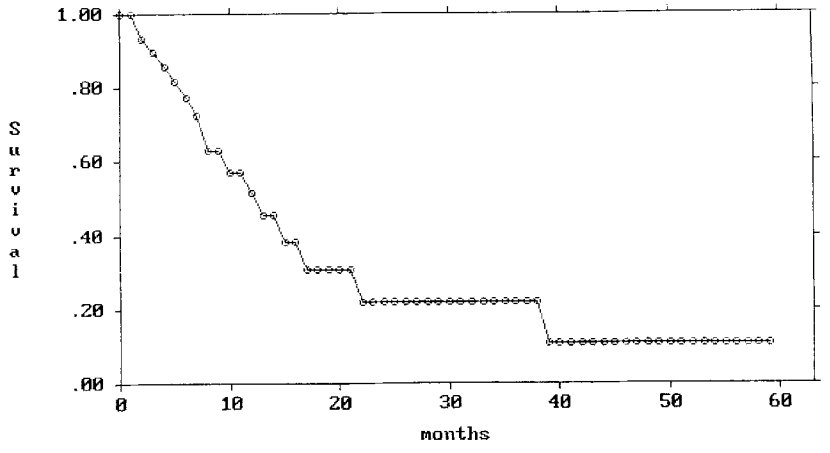

Fig. 3. Survival of patients treated with echinomycin. The median survival as determined by life-table analysis was 12.2 months

Table 3. Response to treatment

	Patients (*n*)
Complete response	0 } 3 (10%)
Partial response	3 }
Stable disease	9 (30%)
Progressive disease	14 (47%)
Not evaluable	4[a] (13%)

[a] 3 patients experienced anaphylaxis during the initial treatment and were removed from study; 1 patient refused a follow-up computed tomographic scan

Response to treatment

As shown in Table 3, there were three partial responders (10%; 90% confidence interval, 3%–23%). Patient 4 presented initially with a Dukes' C colon cancer and underwent a partial colectomy. At 6 months postsurgery he presented with spinal metastases, which were treated initially with radiation therapy and then with a vertebrectomy when they failed to respond to radiation. The patient developed a histologically documented sternal metastasis and abdominal adenopathy 2 months later. Following treatment with echinomycin, the sternal metastasis decreased in size from 6×6 to 4×4 cm and the lymph nodes disappeared.

After receiving three cycles the patient experienced a 3-fold rise in levels of hepatic transaminases that precluded further treatment. He was subsequently treated with 5FU and interferon and achieved a pathologically documented complete remission, and he remains in complete remission at 5 years of follow-up.

Patient 9 underwent a partial colectomy, then experienced a recurrence with histologically documented multiple liver metastases 4 years later (Fig. 1). The patient received 16 courses of echinomycin and achieved a partial response, which persisted for 12 months and was confirmed by a decrease in serum levels of carcinoembryonic antigen from 22 to 12 ng/dl.

Patient 23 underwent a low anterior resection of a rectal lesion, then experienced a local recurrence 1 year later with obstructive symptoms (Fig. 2). Following treatment with echinomycin, the patient achieved a partial response at 2 months, which lasted for 3 additional months.

The five patients who were removed from study for anaphylactic reactions are included as evaluable treatment failures. At a median follow-up of 29 months, the median survival for this patient population was 12.2 months (Fig. 3).

Discussion

We observed 3 objective responses among 30 patients with advanced, recurrent colorectal cancer treated with echinomycin, a bifunctional intercalating agent. It is important to consider that the only active agent currently employed against colorectal cancer is 5FU, and the response rates and survival reported for 5FU in recent trials may not differ from those reported for echinomycin in this trial [13]. Furthermore, the three responses observed in our study were substantial (Figs. 1, 2). It is problematic that in the Southwest Oncology Group trial using a somewhat different schedule [14], 1.2 mg/m^2 echinomycin infused over 15–30 min weekly × 4 followed by 2 weeks rest, no response was observed among 22 evaluable patients, and 55% of the subjects experienced grade 3 gastrointestinal toxicities, with no episode of anaphylaxis being noted. It is also of interest that although patients who received the brief infusion of echinomycin in the earlier portion of our study routinely experienced grade 2–3 emesis, this side effect was markedly ameliorated with the 24-h schedule. As emesis is the dose-limiting toxicity for echinomycin [15], more intensive treatment regimens employing echinomycin with the 24-h schedule should be explored.

It was also of interest that treatment with echinomycin on the schedule employed in our trial resulted in virtually no important hematologic toxicity except for one instance of grade 3 thrombocytopenia, which has previously been reported. Thus, it is likely that echinomycin can be given in combination with other cytotoxic agents without increasing myelosuppression substantially. The anaphylactic reactions, which can probably be attributed to the formulation in Cremophore EL, are worrisome; however, there were no serious consequences for any of the patients being treated, and the incidence of this reaction was reduced using the longer infusion and a premedication schedule similar to that adopted for taxol [16]. Further investigations of echinomycin, alone or in combination with 5FU, in colorectal cancer are warranted using schedules and premedication regimens such as those employed in our study.

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