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ORIGINAL ARTICLE

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A phase I study of 9-aminocamptothecin as a colloidal dispersion formulation given as a fortnightly 72-h infusion

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Abstract *Purpose*: A phase I pharmacologic study was undertaken to determine the maximum tolerated dose (MTD), to characterize the pharmacokinetic profile, and to evaluate all toxicities of the aqueous colloidal dispersion formulation of 9-aminocampothecin (9-AC). *Methods*: 9-AC was administered as a constant 72-h i.v. infusion every 2 weeks to adult cancer patients at dose rates ranging from 25 to 59 μg/m^2 per hour. *Results*:Twenty patients with refractory solid tumors received a total of 86 courses of 9-AC at four dose levels. Myelosuppression, particularly granulocytopenia, was the most common toxicity. Two of six assessable patients entered at 59 μg/m^2 per hour had dose-limiting toxicity (grade 3 diarrhea or need for a 2-week treatment delay to permit granulocyte recovery), whereas lower doses were well tolerated. At the recommended dose, 47 μg/m^2 per hour, the average steady-state plasma levels (Cpss) and area under the curve (AUC) of 9-AC lactone and total drug were 15 and 75 n*M*, and 1034 and 4220 n*M*·h, respectively. A moderate correlation was seen between 9-AC lactone AUC and the percentage decrease in granulocytes. *Conclusions*: The recommended phase II dose of 9-AC colloidal dispersion as a 72-h infusion every 14 days is 47 μg/m^2 per hour (1.13 mg/m^2 per day). The Cpss of 9-AC lactone at this dose exceeded the 10 n*M* threshold level for preclinical activity.

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Introduction

9-Amino-20(*S*)-camptothecin (9-AC) is a camptothecin derivative and topoisomerase-I-targeting agent with broad spectrum single-agent activity in animal tumor models [1, 2, 3, 4]. Topoisomerase I is a nuclear enzyme that plays a crucial role in the relaxation of torsionally strained DNA by inducing a transient single strand nick. Unwinding of supercoiled double-stranded DNA is essential for normal DNA replication and RNA transcription. 9-AC forms a drug-stabilized cleavable complex with topoisomerase I, in which the enzyme and drug are covalently bound to DNA at the site of a single strand break [5, 6, 7]. In the presence of ongoing DNA synthesis, collision of the DNA replication fork with these drug-stabilized cleavable complexes leads to DNA double strand breaks, a cytotoxic event.

Like other camptothecin compounds, 9-AC has a highly labile terminal lactone ring that undergoes nonenzymatic hydrolysis in aqueous solutions to form the less-active open-ring carboxylate [5, 7]. The drug has poor aqueous solubility. The initial clinical testing of 9-AC lactone employed an i.v. formulation in dimethylacetamide (DMA), polyethylene glycol and phosphoric acid with a 72-h infusion administered every 2 or 3 weeks [8, 9]. The principal dose-limiting toxicity (DLT) was myelosuppression, especially granulocytopenia, and the recommended dose was 35 μg/m^2 per hour (47 μg/m^2 per hour with granulocyte colony-stimulating factor) every 2 weeks or 45 μg/m^2 per hour every 3 weeks [8]. A more easily administered colloidal dispersion (CD) formulation of 9-AC was subsequently developed for further clinical evaluation.

A 72-h infusion repeated every 2 weeks was employed in this trial based on our previous study using the DMA formulation of 9-AC [8]. The objectives of this study

were to establish the maximally tolerated dose, to determine the pharmacokinetic profile of 9-AC total drug and lactone form, and to evaluate all toxicities of 9-AC given as the CD formulation.

Patients and methods

Patients

Eligibility criteria included an age of 18 years or older, refractory solid tumors, ECOG performance status of 0 to 2, an absolute granulocyte count ≥2000/μl, a platelet count ≥100,000/μl, serum bilirubin ≤ 1.6 mg/dl, SGOT not more than four times the upper limits of normal, and serum creatinine ≤ 1.6 mg/dl. Objectively measurable disease was not required. At least 4 weeks must have elapsed from prior chemotherapy and at least 2 weeks from prior radiation therapy, and the patient had to be fully recovered from all prior toxicities. Patients with soybean allergy were ineligible for the study. This study had the approval of the Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis (DCTD), NCI (Bethesda, Md.), and of the local institutional review boards; all patients gave written, informed consent.

Dosage and drug administration

Based on our prior experience with the DMA formulation of 9-AC, the starting dose of 9-AC-CD was 25 $\mu g/m^2$ per hour for 72 h. The treatment cycle was repeated every 2 weeks if blood counts permitted and all non-hematologic toxicities had resolved. At least three new patients were evaluated at each dose level. The dose escalation scheme was adopted from our previous trial, with dosage increments of 40%, 33%, and 25% thereafter. Dose escalation proceeded until two of six patients at a given dose level experienced a DLT, defined as a granulocyte nadir < 500/μl either lasting for 5 days or more or complicated by fever, a platelet nadir < 25,000/μl, grade 3 or greater non-hematologic toxicity, or if therapy could not be resumed for two or more weeks due to unresolved toxicities. The NCI common toxicity criteria version 1.0 were used. If no patients at a given dose level had a DLT, then three new patients were entered at the next higher dose level. If a DLT occurred at one dose level, up to three additional patients were entered at that level. Occurrence of a DLT in a second patient at a given dose level indicated that the maximum tolerated dose had been exceeded. Three to six additional patients were to be entered at the preceding dose level to establish the recommended dose.

9-AC-CD was supplied by the DCTD, NCI, as 1- or 2-mg vials, together with one 50-ml vial of diluent containing 20% dextrose, 0.9% sodium chloride, and sterile water in 50- or 100-ml vials. Each 1-mg vial of 9-AC-CD also contained 56 mg dimyristoylphosphatidyl choline, 24 mg dimyristoylphosphatidyl glycerol, and 100 mg mannitol. Before administration, the drug was reconstituted to a concentration of 100 μg/ml using the special diluent. The reconstituted drug was transferred into a 50- or 100-ml Deltec CADD-1 pump (Pharmacia Deltec, St Paul, Minn.) and further diluted with the special diluent required to obtain the volume necessary to administer the dose, using a concentration as close to 20 μg/ml as was practical. Pumps were refilled with fresh solution prepared every 24 h. The drug was administered via an indwelling central venous catheter.

Pretreatment and follow-up studies

All patients had a complete blood count with WBC differential twice weekly, as well as weekly chemistries including metabolic, renal and liver function tests. History and physical examinations were performed before each course. Tumor measurements were performed every third course. A complete response was defined as the complete disappearance of all evidence of tumor and return of abnormal blood tests to normal levels for a minimum of 4 weeks. A partial response was a decrease by at least 50% in the sum of the products of the perpendicular diameters of all measured lesions in the absence of progression of any lesion or the appearance of any new lesions for at least 4 weeks. Stable disease was a change in measurable disease too small to meet the requirements for partial response or progression and the appearance of no new lesions for a period of at least 12 weeks provided there was no worsening of symptoms. The development of any new areas of malignant disease or a > 25% increase in any pretreatment area of disease constituted disease progression. Treatment was continued indefinitely in the absence of disease progression provided the patient tolerated the therapy and wished to continue.

Pharmacologic studies

Blood samples from a peripheral vein were collected into 10-ml heparinized tubes before therapy, at 1, 2, 4, 6, 8, 24, 48 and 72 h from the start of the infusion, and at 0.5, 1.5, 2.5, 4, 5.5, 7.5 and 23 h after completion of the infusion. Clinical sample processing and quantitation of 9-AC lactone and total drug were performed using our previously reported validated assay which uses immediate solid-phase extraction of the sample to separate the lactone from the open-ring carboxylate [10]. The lower limit of quantitation of 9-AC lactone was 0.25 nmol/l (0.09 ng/ml) and of 9-AC total drug was 2.5 nmol/l (0.9 ng/ml). Non-compartmental analytic methods were used to assess the pharmacokinetic data using WinNonLin version 4.0 software (Pharsight, Mountain View, Calif.). The terminal elimination rate constant (k) was estimated by log-linear regression of the terminal portion of the plasma concentration versus time curve. The terminal half-life was calculated from the equation: $t_{1/2} = 0.693/k$. The area under the concentration curve (AUC) was calculated using the linear trapezoidal rule up to the last measurable data point.

Statistical and graphical analysis

Graphs were prepared using SigmaPlot 8.0 for Windows software (SPSS, Chicago, Ill.). The strength of the linear association between pairs of variables was determined by the Pearson correlation coefficient: r values ≥0.70 indicate a strong correlation, r values in the range 0.50 to 0.70 indicate a moderate correlation, and r values in the range 0.3 to 0.5 indicate a weak to moderate correlation.

Results

Twenty patients with refractory solid tumors received a total of 86 courses of 9-AC at four dose levels. The majority had tumors arising in the gastrointestinal tract, and were either asymptomatic or had minor cancer-related symptoms (Table 1). The median number of courses per patient was 3 (range 1 to 12). The median time to treatment failure for all patients was 56.5 days (range 13–161 days). No partial responses were seen among 15 assessable patients with measurable disease, although four patients (27%) had stable disease for 3 months or longer.

Clinical toxicity

Myelosuppression was the predominant toxicity. During the initial cycle of therapy, no patients treated with

Table 1 Patient characteristics

Age (years)	
Median	54.5
Range	36–73
Sex	
Female	9
Male	11
Performance status	
0	4
1	15
2	1
Histology	
Colorectal	12
Lung	3
Breast	2
Pancreas	2
Gastric	1
Prior radiation	8
No. of prior chemotherapy courses	
One	10
Two or three	7
Four to six	3

either 25 or 35 μg/m^2 per hour experienced appreciable toxicity. One of eight patients ultimately enrolled at 47 μg/m^2 per hour experienced grade 4 granulocytopenia during cycle 1, but this was not considered dose-limiting since the count remained below 500/μl for fewer than 5 days. At 59 μg/m^2 per hour, two of six patients experienced DLT consisting of either grade 3 diarrhea or the need for a 2-week delay before therapy could resume to allow the granulocyte count to recover above 1500/μl. The hematologic toxicities experienced during the initial cycle are summarized in Table 2.

Patients who experienced DLT at any time had the dose of 9-AC reduced for the subsequent cycle. The worst hematologic toxicities experienced by each patient per dose level are shown in Table 3. Of 12 patients who received one or more cycles at 47 μg/m^2 per hour, 4 experienced a granulocyte nadir < 500/μl, but this was considered dose-limiting in only one patient (duration ≥5 days). At this dose, only one patient (8%) had grade 3 thrombocytopenia, and 80% of the cycles could be resumed on time. Three of six patients who received one or more cycles at 59 μg/m^2 per hour ultimately had DLT consisting of either granulocytopenia complicated either by fever (one patient) or the need for a 2-week delay to permit recovery (two patients). No instances of grade 4 leukopenia, thrombocytopenia or anemia were observed.

Non-hematologic toxicity (Table 4) consisted primarily of nausea or vomiting (prophylactic antiemetics were not employed), diarrhea and fatigue. With few exceptions, these were generally of mild-moderate severity. At the two highest dose levels, only 2 of 18 patients (11%) experienced grade 3 diarrhea (during cycles 1 and 8, respectively).

Table 2 Hematologic toxicity during the initial cycle. The data are presented as median (range)

9-AC dose (μg/m^2/h)	No. of patients	WBC (×10^3/μl)	Granulocytes (/μl)	Platelets (×10^3/μl)	Decrease in hemoglobin (g/dl)
25	3	6.3 (5.5–12.7)	4,565 (4,246–10,668)	224 (178–376)	1.1 (0.7–3.0)
35	3	4.8 (3.8–6.4)	3,902 (2,205–4,928)	161 (118–280)	1.6 (1.0–1.9)
47	8	3.45 (1.7–5.8)	2,192 (272–4,814)	212 (126–309)	1.85 (1.1–3.8)
59	6	4.5 (1.2–5.8)	3,070 (600–4,251)	169 (37–357)	2.1 (0.7–2.7)

Table 3 Worst hematologic toxicity per patient per dose level. The numbers of patients with each toxicity grade are shown

9-AC dose (μg/m^2/h)	No. of patients	WBC			AGC			Platelets			Hemoglobin		
		Gr 2	Gr 3	Gr 4	Gr 2	Gr 3	Gr 4	Gr 2	Gr 3	Gr 4	Gr 2	Gr 3	Gr 4
25	3	0	0	0	0	0	0	0	0	0	2	0	0
35	6	1	0	0	1	1	0	0	0	0	4	0	0
47	12	4	6	0	0	3	4	0	1	0	5	5	0
59	6	2	2	0	1	2	1	0	2	0	3	2	0

Table 4 Worst non-hematologic toxicity per patient per dose level. The numbers of patients with each toxicity grade are shown

9-AC dose (μg/m^2/h)	No. of patients	Nausea/vomiting			Diarrhea			Fatigue		
		Gr 1	Gr 2	Gr 3	Gr 1	Gr 2	Gr 3	Gr 1	Gr 2	Gr 3
25	3	2	1	0	1	0	0	0	2	0
35	6	2	3	0	2	1	0	2	2	0
47	12	6	3	1	5	3	1	1	9	0
59	6	4	1	0	3	0	1	5	0	0

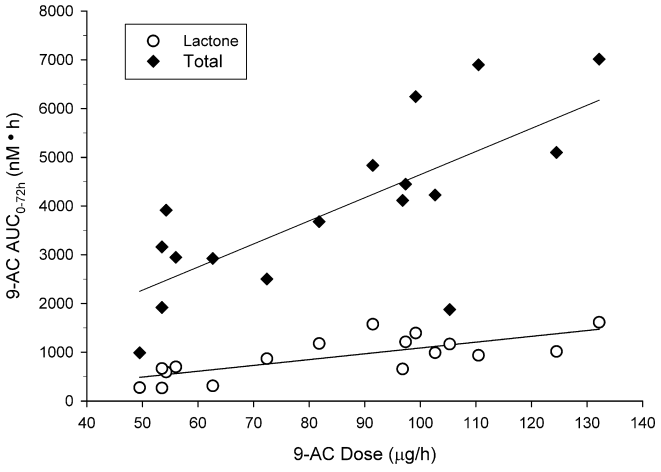

Fig. 1 9-AC AUC from 0–72 h as a function of dose rate. The Pearson Product Moment correlation coefficients were 0.817 ($P < 0.0001$) and 0.641 ($P = 0.0056$) for lactone and total drug, respectively

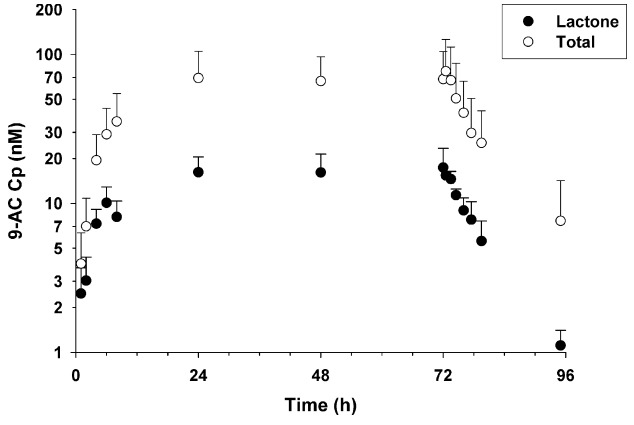

Fig. 2 Plasma concentrations of 9-AC lactone and total drug as a function of time in six patients receiving 47 μg/m^2 per hour. The data are shown as the means ± SD

Pharmacokinetics

Complete pharmacokinetic samples were obtained in 17 patients. The reasons for incomplete sampling included poor venous access (two patients) and the need to discontinue the infusion after 24 h due to a malfunctioning port (one patient). The $AUC_{0-72\ h}$ increased in proportion to increasing 9-AC dose for both 9-AC lactone ($r = 0.817$) and total 9-AC ($r = 0.641$; Fig. 1). Similar results were seen with Cpss and 9-AC dose. During the 72-h infusion, both 9-AC total and lactone plasma levels appeared to approach steady-state by 24 h (Fig. 2). After completion of the 72-h infusion, the lactone form appeared to be cleared faster than total drug. A summary of the pharmacokinetic parameters can be found in Table 5. The average ratio between the lactone form and total drug was 0.24 ± 0.12. Pharmacodynamic analysis indicated that the best correlation was between the AUC

Table 5 Pharmacokinetic parameters. The data are presented as the means ± SD; the numbers of patients at each dose level were as follows (μg/m^2/h): 25 $n = 3$, 35 $n = 3$, 45 $n = 6$, 59 $n = 5$. The Cpss represents the average of the 24-, 48- and 72-h plasma levels

Parameter	9-AC dose (μg/m^2/h)	9-AC lactone	9-AC total
Cpss (n*M*)	25	6.6 ± 4.1	33.5 ± 19.2
	35	8.8 ± 3.9	56.5 ± 11.5
	47	16.6 ± 4.6	68.0 ± 32.4
	59	20.4 ± 4.8	80.8 ± 16.5
$AUC_{0-72\ h}$ (n*M*·h)	25	403 ± 229	2023 ± 1089
	35	535 ± 201	3263 ± 566
	47	1034 ± 264	4220 ± 2001
	59	1282 ± 299	5126 ± 1109
Terminal half-life (h)	25–59	4.79 ± 1.95	7.73 ± 3.11
Vss observed (l/m^2)	25–59	84.7 ± 27.6	26.6 ± 12.5
Clearance (l/h/m^2)	25–59	9.19 ± 3.11	2.31 ± 1.00

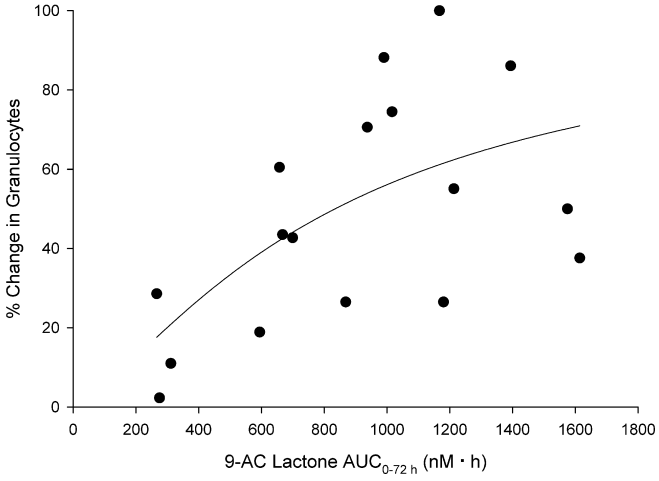

Fig. 3 Percent change in granulocyte count as a function of 9-AC lactone $AUC_{0-72\ h}$. The correlation coefficient was $r = 0.608$

of 9-AC lactone and the percentage decrease in granulocyte count during cycle 1 ($r = 0.608$; Fig. 3); the 50% effective AUC was 834 n*M*·h. The correlation between 9-AC lactone and the percentage decrease in platelet count was only modest ($r = 0.5.12$; 50% effective AUC 1151 n*M*·h), presumably due to the lesser degree of platelet toxicity.

Discussion

We sought to determine the pharmacokinetics, clinical toxicity and a recommended dose of 9-AC given as a CD formulation, which has the advantages of higher stability and increased ease of administration in standard i.v. fluids. Animal toxicology studies suggested that the CD formulation of 9-AC might be equivalent or slightly better tolerated than the DMA formulation. We found that 47 μg/m^2 per hour 9-AC-CD for 72 h every 2 weeks was well tolerated and it is recommended for future studies. When the worst hematologic toxicity per patient

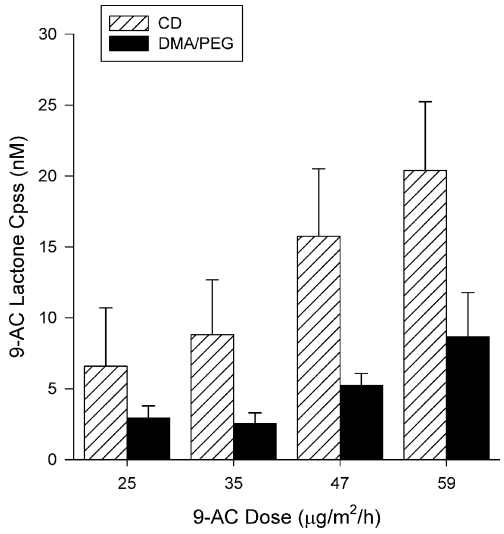

Fig. 4 The Cpss values (average of the 24-, 48- and 72-h Cp) of 9-AC lactone are shown from patients receiving either the CD (current trial) or the DMA formulation (previous trial). The data are presented as the means ± SD; for the CD formulation (current trial) and DMA formulation (previous trial), respectively, the numbers of patients were as follows (μg/m^2 per hour): 25, $n = 3$, 3; 35, $n = 3$, 3; 45, $n = 7$, 15; 59, $n = 5$, 13 (CD and DMA, respectively)

per dose level was compared with our previous results with the 9-AC DMA-PEG formulation, the CD formulation seemed to be associated with less myelosuppression: the incidence of grade 4 granulocytopenia was about half that observed with 9-AC-DMA at the combined 47 and 59 μg/m^2 per hour dose levels (27.8% vs 58.3%) [8]. The recommended dose was 33% higher in the current trial. Of interest, the 9-AC lactone Cpss levels at the four dose levels employed in this current study appeared to be substantially higher than we observed with the DMA formulation (Fig. 4). In contrast, in another trial in which 9-AC-CD as a 72-h infusion every 3 weeks was evaluated, a similar toxicity profile was seen and the same dose compared to their prior trial using the same schedule with the DMA formulation was recommended [11]. Given the relatively small numbers and heterogeneity of the patient population, and the interpatient variability in 9-AC pharmacokinetics, any conclusions about whether the CD formulation affects either the toxicity or lactone pharmacokinetics of 9-AC remain speculative.

Based on the impressive preclinical activity of 9-AC against a variety of human tumor xenografts, this compound was selected for clinical development by the NCI in 1989. Testing in humans was delayed for several years due to difficulties in establishing a suitable formulation for i.v. administration. Initial clinical trials used the DMA formulation of 9-AC. The first schedule tested was a 72-h infusion, based on preclinical studies suggesting schedule-dependant activity, with superior results when the concentration of 9-AC lactone exceeding 10 n*M* for 24 h. On this schedule, granulocytopenia was prominent, although thrombocytopenia was also problematic in heavily pretreated patients with lymphoma and breast cancer. Phase II clinical trials using a 72-h infusion of 9-AC given every 2 or 3 weeks with or without G-CSF support have indicated activity of 9-AC in patients with refractory ovarian cancer, lymphoma, and breast cancer, but its activity in colorectal cancer and non-small-cell lung cancer patients with no prior chemotherapy for metastatic disease has been disappointing [12, 13, 14, 15, 16, 17, 18, 19]. Since preclinical data suggest that more prolonged exposure is more efficacious [20, 21], other schedules of 9-AC have been developed. With a weekly 120-h infusion, the recommended doses are either 25 or 20 μg/m^2 per hour for 2 of 3 weeks or 3 of 4 weeks, respectively [22].

Following the disappointing results with the weekly 120-h infusion schedule of 9-AC in phase II trials in patients with colorectal and non-small-cell lung cancers [23, 24], further clinical development of this drug on all schedules has been stopped by the pharmaceutical sponsor. However, further research into other novel concepts and modes of delivery are being pursued. For example, several 9-AC prodrugs are currently in clinical or preclinical development. 9-Nitro-camptothecin (Rubitecan, SuperGen, Dublin, Calif.), an oral prodrug of 9-AC, has shown apparent clinical benefit in patients with pancreatic cancer whose disease has progressed on prior gemcitabine [25]. This drug is currently in phase III trials both as first- and second-line therapy of patients with pancreatic cancer, and is in phase II testing in several other tumor types. Other novel approaches include 20-carbonate-linked prodrugs of 9-AC designed for activation by tumor-associated plasmin [26], targeted polymeric bioconjugates based on *N*-(2-hydroxypropyl) methacrylamide copolymers [27], 9-AC glucuronide (which may display selective antitumor activity against tumors that overexpress beta-glucuronidase) [28], and enzyme-activated prodrug therapy to enhance tumor-specific replication of adenovirus vectors that express a secreted form of beta-glucuronidase [29].

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