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Phase I study of adozelesin (U-73,975) in patients with solid tumors

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During a phase I clinical and pharmacologic trial, 26 patients with refractory solid tumors were treated with increasing doses of adozelesin by brief intravenous infusion every 3 weeks. Overall, adozelesin was well tolerated. The dose-limiting toxicity was myelosuppression, mainly thrombocytopenia and leukopenia. Non-hematologic toxicity was generally mild, with fatigue (36%), local reaction at the infusion site (24%), nausea or vomiting (20%) and hypersensitivity reaction (16%) being the most common adverse effects. There were no objective clinical responses. The maximally tolerated dose on this schedule was 188 μg/m² with the recommended phase II starting dose being 150 μg/m² on an every 3 week schedule. Adozelesin merits broad investigation at the phase II level.

Key words: Adozelesin, chemotherapy, phase I, U73,975.

Introduction

Adozelesin is a novel compound that belongs to a unique class of DNA-sequence-specific agents, the cyclopropa[*c*]pyrrolo[3,2-*e*]indol-4(5H)-ones (CPI), which are modeled on the antibiotic CC-1065 (Figure 1). CC-1065, the lead compound of this series, was originally isolated from broths of *Streptomyces zelensis*.[1] Compared with this parent compound, adozelesin has been found to have higher potency, greater absolute efficacy and a lower toxicity profile.[2–4] Adozelesin has been shown to be active in almost every common murine tumor model,[5] including xenografts of human cancer in nude mice. It has also been found to be much more potent than doxorubicin, cisplatin, 5-fluorouracil and cyclophosphamide in human gynecologic cancer cell lines.[6]

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In an initial phase I trial, adozelesin was administered to patients with solid tumors refractory to standard therapy at a conservative starting dose of 1/30 of the LD_{10} in mice (10 $\mu g/m^2$) by brief infusion every 6 weeks. Preliminary data suggest a relatively short biological half-life, although pathways of metabolism and elimination have not been defined. Based on the available information, we conducted a phase I clinical and pharmacologic trial of adozelesin in patients with drug-refractory or advanced solid tumors with the following objectives: (i) to determine the maximally tolerated dose (MTD) of adozelesin administered by a brief intravenous infusion every 3 weeks, (ii) to evaluate its quantitative and qualitative clinical toxicities, (iii) to investigate its pharmacologic characteristics, and (iv) to evaluate its antitumor effect in patients with advanced cancer.

Patients and methods

Patient selection

All patients had histologic proof of advanced solid tumors refractory to standard treatment, a performance status of ≤ 2 (ECOG) and an anticipated life

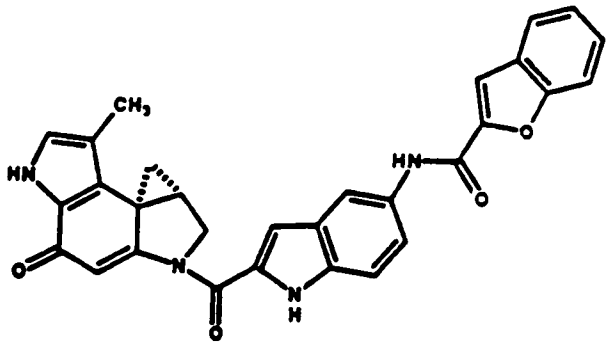

Figure 1. Structure of adozelesin.

expectancy of $\geqslant 12$ weeks. Measurable disease, while desirable, was not required. Patients were required to have adequate bone marrow function (total white cell count $>4000/mm^3$ and platelets $>100\,000/mm^3$), liver function (total bilirubin <2.0 mg/dl, normal transaminases) and renal function (creatinine <2.0 mg/dl). In addition, patients had to have a normal carbon monoxide diffusion capacity (DLCO) and chest auscultation. All patients were informed as to the experimental nature of the study and signed an informed consent in accordance with institutional and federal guidelines.

Pretreatment evaluation and follow-up studies

Before each course of treatment, a complete history and physical examination were performed. Laboratory studies included complete blood count, serum electrolytes, BUN, creatinine, glucose, calcium, phosphate, total bilirubin, AST, ALT, LDH, alkaline phosphatase, albumin, total protein, uric acid and CPK, urinalysis, chest radiograph and ECG. Pulmonary function tests including chest auscultation, a 1 min respiration rate, DLCO, baseline spirometry and arterial blood gases on room air were also performed. With the exception of the 1 min respiration rate and DLCO, which were obtained every 3 weeks, all routine laboratory studies noted above were obtained weekly. Spirometry was performed prior to each course and in those patients developing respiratory problems. Appropriate studies were performed every 6 weeks to evaluate tumor response.

Study design

A minimum of three patients were treated at each dose level and observed for at least 3 weeks before subsequent patients were enrolled at that level. Patients without evidence of toxicity after 3 weeks were retreated at the same dose level provided that their disease showed no evidence of progression. When significant toxicity (grade 3 or greater) was observed at a given dose level, an additional three patients were treated at that level and subsequent dose levels were escalated by 25% of the preceding dose level. Dose reductions were performed according to Table 1. All patients who received study treatment were evaluated for toxicity.

Criteria for removal of patients from the study included disease progression after two courses of therapy, development of unacceptable toxicity or decision of the patient to withdraw from the study. For graded toxic effects the National Cancer Institute common toxicity criteria were used. The MTD was defined as the dose level at which three or more of six patients developed any grade 3 or greater toxicity. An additional four patients had to be treated at a dose one level lower than the MTD and at least three of ten patients were to receive a minimum of three courses each at this dose level to ascertain whether or not there was cumulative toxicity.

Table 1. Dose adjustment

Platelet nadir (cells/mm^3)	Total WBC nadir (cells/mm^3)		
	>300	1000–3000	<1000
>75 000	no change	75%[a]	50%[a]
25–75 000	75%[a]	75%[a]	50%[a]
<25 000	50%[a]	50%[a]	off study

[a] Percent of previous dose given.

Drug administration

The starting adozelesin dose level was 30 $\mu g/m^2$ administered every 3 weeks followed by a 21 day observation period, which defined one treatment course. The drug concentrate was diluted to 1/10 strength (0.1 mg/ml) with a polyethylene glycol vehicle and the appropriate dose was given as a 10 min infusion via an intravenous line containing 5% dextrose in water. All treatment cycles were administered in the outpatient setting.

Results

Patient characteristics

A total of 26 patients were entered into this trial. Patient characteristics are outlined in Table 2. One patient developed a severe adozelesin-related adverse reaction and discontinued study drug prior to receiving the full dosage. Twenty-five patient were evaluable for toxicity. Twenty patients completed at least two courses of therapy, had measurable disease and were therefore assessable for response. There were eight males and 18 females, with a median age of 60 years (range 40–77 years). Eleven patients (42%) had colorectal cancer; the

Table 2. Patient characteristics

	No. of patients
Patients entered	26
Accessibility	
toxicity	25
response	21
Median age, years (range)	65 (40–77)
Sex	
male	8
female	18
Performance status (ECOG)	
0	17
1	8
2	0
	(1 not reported)
Primary site	
colorectal	11
ovarian	4
lung	2
soft tissue sarcoma	3
cervix	1
parotid	1
renal	1
bile duct	1
unknown	2
Previous therapy	
surgery	21
chemotherapy	26
radiation	7

remainder had lung, ovarian, cervix, parotid, renal, bile duct cancer, sarcoma or unknown primary malignancy. All patients had received some form of prior therapy and had a ECOG performance status of 0 or 1 (except for one patient with an unreported performance status).

Toxicity

Five dose escalations were required to define the MTD. One patient had to be removed early from the study because of a severe adozelesin-related allergic reaction. While on study, only one patient died of progressive disease.

Adozelesin was generally well tolerated. A summary of the hematologic toxicity data is presented in Tables 3 and 4. The dose-limiting toxicity was myelosuppression, characterized by thrombocytopenia and leukopenia. Non-limiting anemia was also observed. Nadir counts of leukocytes and platelets occurred between days 5 and 31. In most patients, recovery had occurred by day 21 of each cycle and dosing delays were rare. One patient who was treated at the 100 $\mu g/m^2$ dose level had to have treatment postponed for 1 week because of grade 2 leukopenia. In three of five patients entered at the 188 $\mu g/m^2$ dose level, grade

Table 3. Hematologic toxicity ($\leq$grade 2 except as noted)

Dose ($\mu g/m^2$)	No. of patients	Leukopenia	Anemia	Thrombocytopenia
30	3	1	1	0
60	4	0	0	1
100	3	1	0	1
150	10	2	2	3
188	5	3	1	3 (2 grade 3,
		3 (grade 1)		1 grade 4)

Table 4. Hematologic toxicity (grade 3 or 4)

Dose ($\mu g/m^2$)	No. of patients	No. of patients with			
		WBC		Plt $\leq$ 50 000/mm^3	Hb $\leq$ 8.0 g/dl
		$\leq$2000/mm^3	$\leq$1000/mm^3		
30	3	0	0	0	0
60	4	0	0	0	0
100	3	0	0	0	0
150	10	0	0	0	0
188	5	1	0	3	0

3 and 4 thrombocytopenia (platelets $< 50\,000/mm^3$) developed during the first or second course of therapy and consequently the study was terminated at this dose level. One of these three patients had a platelet count of $15\,000/mm^3$ following his second course of therapy and died of renal failure due to rapidly progressive disease on day 21. Grade 3 leukopenia (WBC $< 2000/mm^3$) occurred in only one of the five patients treated at the 188 $\mu g/m^2$ dose level. Two patients required a 75% dose reduction for grade 2 leukopenia at the 100 and 150 $\mu g/m^2$ dose levels. Decreased hemoglobin levels were seen in three patients although grade 3 or greater anemia (Hb < 8 gm/dl) was not observed in only one patient at the 188 $\mu g/m^2$ dose level. Cumulative myelosuppression did not occur in any patient regardless of dose level. No patient required hospitalization for neutropenic fever. Platelet transfusions were required in only one patient who developed grade 4 thrombocytopenia ($15\,000/mm^3$) with epistaxis during his second course of therapy at the 188 $\mu g/m^2$ dose level (*vide supra*). No other incidences of thrombocytopenia-related bleeding occurred.

Non-hematologic adverse effects related to adozelesin are summarized in Table 5. Tolerance to the drug was generally good, with most non-hematologic toxicities being mild to moderate (grade 1 or 2). The most common side-effects were fatigue (36%) and a local reaction characterized by erythema and/or burning sensation at the infusion site (24%). Despite its common occurrence, fatigue was generally mild and not incapacitating with the exception of one patient who experienced impaired performance status at the 100 $\mu g/m^2$ dose level. Mild to moderate nausea or vomiting occurred in five patients (20%). Four patients (16%) had a hypersensitivity reaction following adozelesin infusion characterized by transient dyspnea, wheezing, facial flushing and generalized pruritus. Adozelesin administration was interrupted in two patients because of moderate to severe (grade 3) hypersensitivity reactions. One of these events occurred during a patient's second course at the 30 $\mu g/m^2$ dose level and the other during a patient's first course at the 188 $\mu g/m^2$ dose level. Blood pressure fall or other hemodynamic adverse effects were not observed and no specific measures other than the administration of antihistamine drugs (diphenhydramine) to an occasional patient were required.

Table 5. Non-hematologic toxicity ($\leq$grade 2 except as noted)

	Dose ($\mu g/m^2$)					
	30 ($n = 3$)	60 ($n = 4$)	100 ($n = 3$)	150 ($n = 10$)	188 ($n = 5$)	total ($n = 25$)
Alopecia	0	0	1	1	0	2
Anorexia	0	1	0	1	0	2
Back pain	1	0	1	1	0	3
Chest discomfort	1	0	0	0	0	1
Diarrhea	2 (1 grade 3)	0	0	0	0	2
Dyspnea	0	0	0	0	2	2
Fatigue	2	1	2	3	1	9
Headaches	0	0	0	1	1	2
Hyperglycemia	0	0	1	0	0	1
Hypersensitivity[a]	1 (grade 3)	0	0	1	2 (1 grade 3)	4
Hypoglycemia	0	0	1	0	0	1
Hyponatremia	0	1	0	0	0	1
Local reaction[b]	0	0	0	4	2	6
Mental status changes	0	0	1 (grade 3)	1	0	2
Mucositis	0	0	0	3	1	4
Nausea or vomiting	3	1	0	0	1	5
Visual disturbances	1	0	0	0	0	1

[a]A patient who began his first course of treatment at the 188 $\mu g/m^2$ dose level and required drug discontinuation because of a moderate to severe (grade 3) adozelesin-related hypersensitivity is included in the cases of hypersensitivity, but not in the remainder of the table due to early removal from the study.
[b]Erythema and/or burning sensation at infusion site.

Other side effects were mucositis (16%) and back pain (12%).

Response

No objective response occurred seen in any of the 20 patients who were evaluable for response. Most patients had progressive disease after a median of two courses of therapy.

Discussion

This report describes our initial experience with the novel antibiotic, antitumor compound adozelesin in patients with solid tumors refractory to standard therapy. The drug was generally well tolerated over the range of doses tested. The dose-limiting toxicity was myelosuppression, mainly thrombocytopenia and leukopenia.

The MTD was 188 $\mu g/m^2$. At this dose level, platelet counts of $<50\,000/mm^3$ (grade 3 or 4 thrombocytopenia) were encountered in three of five patients. Leukopenia was generally moderate ($\leq$ grade 2) and required dose reduction in only two patients. Cumulative myelosuppression was not observed in this study.

The most common non-hematologic toxicities were mild fatigue, local reaction at the infusion site, mild to moderate nausea or vomiting and drug-related hypersensitivity. These adverse effects did not appear to be dose dependent. Only two patients had to be removed from the study due to grade 3 toxicity from adozelesin-related hypersensitivity.

Adozelesin has been shown to be active in preclinical studies using experimental tumor models[5] and human cancer cell lines.[6] In the present study, however, no objective tumor responses were seen at the dose levels administered.

Conclusion

Adozelesin can be administered safely and is generally well tolerated. The proposed starting dose of adozelesin for phase II trials is 150 $\mu g/m^2$ given as a 10 min intravenous infusion every 3 weeks. Since adozelesin was not associated with major organ toxicities, with the exception of myelosuppression, it could be useful in the treatment of hematologic malignancies and as a component of high dose ablative chemotherapy in bone marrow transplantation protocols. Despite the lack of objective responses in the present study, the toxicity profile and clear *in vitro* antitumor activity of adozelesin justify its continued clinical evaluation.

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