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Research paper

Phase II study of adozelesin in untreated metastatic breast cancer

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Adozelesin is the first of a class of DNA-sequence-selective alkylating agents, the cyclopropa(c)pyrrolo(3,2-e)indol-4(5H)-ones (CPIs), that have been shown to have of potent inhibitory properties of DNA synthesis. Based on preliminary data from phase I studies showing clinical activity in patients with breast cancer, we initiated a multicenter phase II study in untreated metastatic breast carcinoma. Adozelesin was administered at a starting dose of 150 $\mu g/m^2$ as a single 10 min infusion per course, repeated every 4 weeks, for up to 1 year of treatment. It was planned that at least 25 patients should be accrued but the trial was stopped early because of slow accrual and lack of efficacy as demonstrated by the infrequency of objective responses. Seventeen patients were enrolled in this study, only 14 were evaluable, the following responses were observed: one partial response (7%), three stable diseases (22%) and 10 progressive diseases (71%). Myelosuppression was the most frequent adverse event; one patient died of pulmonary complications. We conclude that adozelesin has marginal efficacy in the treatment of metastatic breast cancer at the dosage and schedule used in this study. [© 1998 Lippincott Williams & Wilkins.]

Key words: Adozelesin, metastatic breast cancer, phase II.

Introduction

Metastatic breast cancer is an incurable disease and palliation must be considered the main goal when treating these patients.[1] The introduction of new drugs, in particular the taxanes, has been associated with improved objective response and has translated in marginal prolongation of survival.[2,3]

Adozelesin (U-73975) is the first of a class of DNA-sequence-selective alkylating agents, the cyclopropa(*c*)pyrrolo(3,2-*e*)indol-4(5*H*)-ones (CPIs), which are modeled on the antibiotic CC-1065.[4]

CC-1065, the lead component, was originally isolated from broths of *Streptomyces zelensis*.[5,6] Compared with this parent compound, adozelesin has shown greater efficacy, being active in common murine tumor models, including xenographs of human cancer in nude mice.[7]

The CPIs are potent inhibitors of DNA synthesis and stabilize the native B-form DNA helix by binding in the minor groove; they do not bind to denatured or single-stranded DNA or to RNA or protein. The cytotoxicity of the CPIs is greatest for mitotic cells, less for G_1/S phase cells and least for G_2 phase cells.[7] Based on its preclinical level of activity and novel mechanism of action, adozelesin has been viewed as an agent with high potential for clinical development.[8]

Adozelesin was the first CPI to enter clinical trials and phase I studies showed that it was well-tolerated in solid tumor patients.[9–14] The drug was tested in four different phase I studies involving patients with a mixed group of solid tumors, including a total of eight heavily pretreated breast cancer patients. Of six evaluable patients, two had progressive disease (PD), and four demonstrated stable disease (SD) or minor response (MR) of 20, 9, 6 and 4 weeks duration. Based on these preliminary data indicating antitumor activity, we designed this study to evaluate the therapeutic efficacy of adozelesin in chemotherapy-naïve patients with measurable metastatic breast cancer.

Patients and methods

Study design

The trial was designed as a non-randomized, non-controlled, open-label, single-dose, multiple course,

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multicenter phase II study to evaluate whether adozelesin given as a monthly i.v. infusion produces objective clinical responses in adult patients with previously untreated measurable metastatic breast carcinoma. Initially, 25 evaluable patients with chemotherapy-naïve measurable metastatic breast carcinoma were to be accrued. If four or fewer of the 25 evaluable patients achieved an objective response (CR + PR), then the study would have been terminated and the drug declared inactive. If an objective response was seen in at least five of 25 patients, a total of 45 evaluable patients would have been accrued to estimate the true response rate. After their initial course, patients would have continued to receive repeated courses of treatment, as long as there was a clear clinical benefit, for a maximum of 1 year.

Study population

Eligibility criteria included histologic documentation of breast carcinoma, measurable metastatic disease and no previous chemotherapy or biologic/immunotherapy for metastatic disease. Patients that had received cytotoxic adjuvant therapy were included if more than 12 months had elapsed after the last adjuvant treatment. For patients exposed to hormonal therapy, patients were included if more than 4 weeks had elapsed since the final hormonal treatment, unless unequivocal PD had been documented at least 2 weeks after the hormonal treatment.

Patients were required to have a Southwest Oncology Group Performance Status $\leqslant 2$ (either 0 = fully active, 1 = restricted to light work or 2 = unable to carry out any work activities but up and about more than 50% of waking hours) and life expectancy of at least 8 weeks. Patients were also required to have adequate organ function which was defined as total WBC $\geqslant 3000/\mu l$, platelet count $\geqslant 100\,000/\mu l$, hemoglobin $\geqslant 10$ g/dl, serum bilirubin level $\leqslant 2.0$ mg/dl, and SGOT and alkaline phosphatase $\leqslant 3.0$.

All premenopausal patients with childbearing potential were required to have a negative pregnancy test at entry and had to use adequate contraceptive methods during the study.

Before entering the study, all patients underwent an evaluation that consisted of a complete medical history, physical examination, chest radiography, bone scan, and liver ultrasonography and other tests required for tumor measurement. All patients signed an informed consent form approved by the Institutional Review Board of the investigating institution before receiving treatment.

Treatment schedule

Adozelesin was provided by Pharmacia & Upjohn (Kalamazoo, MI) in sterile glass ampoules that contained 1.2 ml of drug (1.0 mg/ml) dissolved in PET vehicle (60% polyethylene glycol 400, 30% ethanol and 10% Tween 80). These ampoules were stored at $-20°C$ and protected from light until the time of dilution for patient administration. The dose was drawn into a disposable plastic syringe and injected over a 10 min period through the side-port of a freely flowing i.v. line containing 5% dextrose in water.

The starting dose of adozelesin was 150 $\mu g//m^2$ given as a single infusion per course, with courses repeated every 4 weeks for up to 1 year of treatment for each patient. Based on previous experience from phase I studies myelosuppression was expected to be the most common dose-limiting toxicity. Dose modifications were made for grade $\geqslant 3$ toxicity, according to the World Health Organization (WHO) grading system. A 25 and 50% dose reduction was planned for neutropenia and thrombocytopenia grade 3 or 4, respectively. In view of the greater thrombocytopenia relative to neutropenia induced by adozelesin, hematologic growth factors were not used prophylactically to prevent neutropenia. For non-hematological toxicity, dose reductions were performed following the same scheme: 25% reduction for grade 3 toxicity, 50% reduction or removal from the study for grade 4 toxicity. A minimum of one course was required for a patient to be considered as having received an adequate trial to fully evaluate toxicity.

Methods of evaluation

Blood counts were obtained weekly at baseline and in every patient. A weekly serum BUN, creatinine, glucose, electrolytes, calcium, phosphate, bilirubin (total), AST (SGOT), alkaline phosphatase, ALT (SGPT), LDH, albumin and total protein were also performed. Prior to each course a history and physical examination and response determination were performed. Appropriate studies were repeated every 4–8 weeks and then when indicated to confirm response.

Standard response criteria, as defined by the UICC, were used. Complete remission (CR) was defined as the disappearance of all symptoms and signs of disease for at least 1 month. Partial remission (PR) indicated a greater than 50% decrease in measurable lesions, objective improvement in assessable lesions and no evidence of new lesions. SD required lesions to remain unchanged, including less than 50% increase or

decrease in the size of measurable lesions. PD indicated an increase in the dimensions of measurable or non-measurable lesions or appearance of new lesions. Death from any cause was recorded as failure.

Results

Patients characteristics and response

Seventeen patients were enrolled in five centers. The basic demographic characteristics of the patients and response to treatment are reported in Table 1. The median age of the patients was 58 years (range 37–76) and they received a median of two courses of treatment (range 1–4). Fourteen patients were evaluable for response. The overall response rate was 7%. One patient (7%) achieved a PR, three patients (21%) obtained SD. PD was documented in 11 patients (71%).

Toxicity

All 17 patients were evaluable for toxicity. There was one death in this study. The patient received a total of three courses of treatment, and after the last administration she developed pancytopenia, fever, pulmonary infiltrates, respiratory failure and subsequently died. A fungus was cultured from one of several blood cultures obtained. No autopsy was obtained. Apparently she developed fever and pulmonary infiltrates also after the second course that was presumed to be infectious in origin and resolved with antibiotic treatment. Her death was felt to be drug related due either to an expected hazard of cytotoxic therapy (myelosuppression) or to a lung injury that had been noted in previous phase I studies.[14]

Table 1. Patient demographics, treatment duration and response

Patient	Age	Sex	No. of courses	Response
1	37	F	3	PD
2	65	F	2	PD
3	48	F	1	PD
4	64	F	1	PD
5	46	F	1	NE
6	37	F	4	PD
7	68	F	2	NE
8	58	F	1	PD
9	64	F	2	NE
10	55	F	1	PD
11	58	F	2	PD
12	76	F	3	SD
13	57	F	1	PD
14	44	F	1	SD
15	65	F	4	PR
16	53	F	1	PD
17	74	F	3	SD

NE, not evaluable.

Myelosuppression was reported in 14 patients (82%), and consisted mainly of thrombocytopenia (35%) and neutropenia (29%). Four patients developed respiratory symptoms consisting of respiratory distress with or without evidence of pulmonary infiltrates. Other non-hematologic side effect included: nausea and vomiting (two patients), fatigue, septicemia (one patient), and hypokalemia (one patient).

Discussion

Adozelesin is an analog of the antibiotic CC-1065 isolated from broths of *S. zelensis* and found to have potent antitumor activity in some experimental tumor systems.[4,5]

Adozelesin is a novel alkylating agent that covalently binds to the minor groove of double-stranded DNA at adenine-thymine-rich sites.[7] Preclinical data demonstrated antitumor activity against murine leukemia models and solid tumor models.[8] Phase I studies demonstrated that myelosuppression, in particular thrombocytopenia, was the principle dose-limiting toxicity and sometimes was prolonged.[9–14] Occasional and unexplained episodes of pulmonary toxicity were reported in one study.[14] The recommended dose for phase II studies was 150 $\mu g/m^2$.

In the four different phase I studies a total of eight patients with metastatic breast cancer were enrolled. Of the six evaluable patients, four demonstrated SD or MR.[9–14] These encouraging data prompted this phase II study in untreated metastatic breast cancer. We observed only one PR (7%) of 14 evaluable patients; the majority (71%) progressed while on treatment. Myelosuppression, in particular thrombocytopenia, was the most frequently reported adverse event associated with adozelesin treatment. One death was reported secondary to respiratory failure most likely as a result of infectious complications, but drug-related lung injury could not be excluded.

We conclude that adozelesin at the dosage and scheduled utilized in this study has marginal efficacy in metastatic breast cancer. The results are particularly disappointing in view of the fact that the patients accrued to this trial had not received prior therapy for their metastatic disease.

The concomitant availability of more effective drugs (i.e. Taxol, Taxotere) and the serious toxicity reported

with adozelesin critically affected the accrual into this study and limited the possibility of further investigation of the role of this drug in the treatment of metastatic breast cancer.

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