Cancer Chemother Pharmacol (1992) 30: 321–324

Cancer Chemotherapy and Pharmacology

Phase I trial of a 72-h continuous-infusion schedule of fazarabine*

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Received 11 November 1991/Accepted 23 March 1992

Summary. Fazarabine (Ara-AC), a structural analog derived from the antitumor nucleoside cytosine arabanoside (Ara-C) and 5-azacytidine (5-AC), was studied in a phase I clinical trial. Doses ranging from 0.2 to 2.0 mg m^{-2} h^{-1} were given intravenously over 72 h every 28 days. The maximum tolerated dose (MDT) was 2.00 mg m^{-2} h^{-1}. The dose-limiting toxicity was myelosuppression, with granulocytopenia being quantitatively more important than thrombocytopenia or anemia. Nonhematologic toxicity was minimal. Associated with the solvent dimethylsulfoxide (DMSO) was a bitter taste and a garlic-like odor.

Introduction

Fazarabine (1-β-D-arabinofuranosyl-5-azacytosine, Ara-AC) is a novel compound synthesized by Beisler et al. [1] at the National Cancer Institute. It combines the structural features of two nucleosides, arabinosyl cytosine (Ara-C) and 5-azacytidine (5-AC) [1, 2]. The antimetabolites Ara-C and 5-AC are effective anticancer drugs in the treatment of acute myelogenous leukemia. The molecular structure of fazarabine includes the stereochemical inversion of the hydroxyl group at the 2′ position of cytidine (as in Ara-C) plus the substitution of a nitrogen in place of carbon 5 in the pyrimidine base (as in 5-AC; Fig. 1). Like Ara-C, fazarabine inhibits DNA synthesis. Unlike 5-AC, it causes little, if any, inhibition of RNA formation. Because of the rapid cleavage of the triazine ring, fazarabine is unstable in aqueous media. The solvent dimethylsulfoxide (DMSO), with its inability to participate in the hydrolysis of the triazine ring, improves the stability of fazarabine and is necessary for its intraveneous administration [5].

In preclinical systems, fazarabine demonstrates a broad spectrum of cytotoxicity [3, 4, 6, 9, 10]. Therapeutic activity has been observed against murine and human leukemias, transplantable murine solid tumors, and human tumor xenografts. In comparison with Ara-C and 5-AC fazarabine displays increased therapeutic activity, particularly against solid tumors. Schedule dependence has been demonstrated in mice bearing L1210 leukemia, with superior activity being seen following the frequent administration of multiple doses. However, in a solid tumor model, the antitumor activity did not appear to be superior for continuous infusion of compared with bolus injection [7].

Preclinical toxicology studies indicated that the bone marrow and the gastrointestinal tract were the main target organs. When fazarabine is given as a continuous infusion, the resultant toxicity is related to both the dose and the duration of exposure. Based on this information, we conducted a phase I clinical trial of fazarabine in patients with refractory solid tumors. The major goals of the study were (a) to determine the maximum tolerated dose (MTD) of fazarabine given as a 72-h continuous infusion at 4-week intervals, (b) to describe the qualitative and quantitative clinical toxicity of fazarabine on this schedule, and (c) to seek preliminary evidence of its therapeutic activity in patients with advanced solid tumors.

Patients and methods

Patient population. All patients had histologic proof of advanced solid tumors that were refractory to standard treatment, a performance status of less than or equal to 2 (Zubrod scale), and a life expectancy of at least 12 weeks. Eligibility criteria included an absolute granulocyte count of greater than 1500 cells/mm^3, a platelet count of greater than 100,000 cells/mm^3, creatinine levels of less than 1.5 mg/100 ml, and bilirubin values of less than 1.5 mg/100 ml. Individuals with radiographically detectable brain metastases were eligible if they had received cranial irradiation and the metastases remained stable in the absence of steroid treatment.

* Supported in part by contract NOICM57739, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

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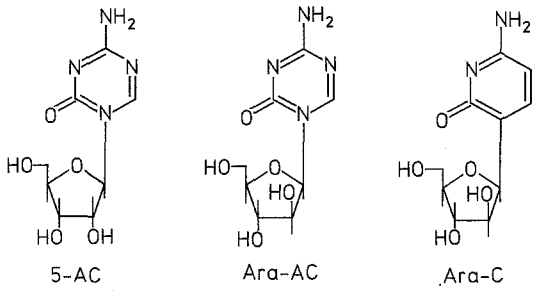

Fig. 1. Molecular structures of 5-AC, Ara-AC, and Ara-C

All patients were evaluated by one of the investigators prior to study entry. A complete history was obtained and a full physical examination, including determinations of height, weight, and performance status as well as clinical tumor measurements (when available), was carried out. Laboratory tests included complete blood counts with differential; platelet counts; determinations of serum electrolytes, blood urea nitrogen, creatinine, glucose, total protein, albumin, calcium, phosphorus, uric acid, alkaline phosphate, total bilirubin, SGPT, SGOT, and coagulation profiles; and urinalysis. A baseline electrocardiogram was obtained. A chest radiograph and appropriate radiologic evaluation of tumor extent was performed. All patients were informed as to the experimental nature of this program and signed an informed consent document in accordance with institutional policies.

Study design. A minimum of three patients who had not previously been exposed to fazarabine were treated at each dose level. Patients treated with doses that were not associated with toxicity were allowed to receive subsequent courses at escalated doses; however, once evidence of toxicity had been documented, patients could not receive escalated doses. When the dose-limiting toxicity had been determined, additional subjects were treated to more completely defined acute accumulative toxicities. Patients who tolerated the therapy continued to receive treatment as long as their underlying tumor showed no evidence of progression. All subjects treated were evaluated for toxicity. Patients were formally evaluated for antitumor response after every two courses of therapy.

Criteria for removal of patients from the study included disease progression, patient noncompliance, a request to withdraw, or the development of unacceptable toxicity. For hematologic toxicities, the MTD was defined as the dose of fazarabine one level below that associated with a granulocyte count of less than 500 cells/mm^3 or a platelet count of less than 50,000 cells/mm^3 in more than one-third of the patients treated at that level. For graded nonhematologic toxicity, World Health Organization criteria were used [7].

Drug information. Fazarabine was supplied by the Division of Cancer Treatment, National Cancer Institute (Bethesda, Md.), as a freeze-dried powder in a ready-to-mix vial with 7.2 ml 70% DMSO. The 24-h fazarabine dose was infused by auto-syringe through polyolefin tubing at a rate of 0.3 ml/h. Since the final concentration of DMSO must be less than 1%, the fazarabine auto-syringe was connected to another intravenous line infusing 5% dextrose and water. This system has been evaluated and found to be adequate for the delivery of greater than 79% of the expected drug dose over 24 h. The auto-syringe containing the drug was changed every 24 h during the 72-h treatment interval [3].

Drug administration. The starting dose was 0.2 mg m^{-2} h^{-1} given intravenously over 72 h every 28 days. This dose represents 1/50th of the safe dose in mice. Toxicity studies completed by the National Cancer Institute [3, 5, 7] predicted the toxicity of fazarabine to be both dose- and schedule-dependent. As such, the dose lethal to 10% of the study population (LD_{10}) was not established; rather, a range of concentrations and infusion durations were tested until toxicity was observed. Murine studies demonstrated that a 72-h infusion of 10.8 mg/m^2 could safely be given without producing toxicity; whereas a 15-mg/m^2 infusion was fatal. Given the low starting dose, the first two dose escalations were 100% increments (from 0.2 to 0.4 to 0.8 mg m^{-2} h^{-1}) and subsequent escalations involved increments of approximately 25% (1.0, 1.2, 1.5, 1.75, and 2.0 mg m^{-2} h^{-1}). All patients were hospitalized. Hematologic parameters were checked twice weekly and biochemical parameters, weekly.

Table 1. Patients' characteristics

Patients entered	37
Patients evaluable	36
Response/toxicity	31
Toxicity only	5
Median age (range)	53 (36–73) years
Sex (M:F)	21:15
Performance status:	
0	2
1	27
2	7
Prior therapy	
None	1
Chemotherapy	34
Radiation	21
Tumor type	
Colorectal cancer	12
Non-small-cell lung cancer	9
Sarcoma	6
Breast cancer	2
Head and neck cancer	2
Melanoma	1
Pancreatic cancer	1
Lymphoma	1
Unclassified adenocarcinoma	1
Unclassified carcinoma	1

Results

Patients' characteristics

A total of 36 patients (21 men and 15 women were entered into this trial 1 additional patient had been registered but never received treatment). The characteristics of the 36 treated subjects are outlined in Table 1. All patients were evaluated for toxicity. In all, 31 individuals completed at least 2 courses of therapy, had measurable disease, and were therefore also evaluable for response. Of the 5 patients who were evaluated for toxicity alone, 3 completed less than 2 courses of therapy and 2 died prior to the response evaluation. The specific diseases treated in this trial included colorectal cancer, 12 patients; non-small-cell lung cancer, 9; sarcoma, 6; breast cancer, 2; head and neck cancer, 2; and other malignancies, 5. A total of 35 patients had received some form of prior therapy, and 29 subjects had a performance status of 0 or 1.

Toxicity

Seven dose escalations were required to define the MTD. A total of 83 courses of fazarabine were given; 7 patients received 3 or more courses, with the maximum being 10

Table 2. Hematologic toxicity

Dose (mg m^{-2} h^{-1})	Patients	Courses	Number of patients with			Median (nadir × 1000)			
			AGC <900 cells/mm^3	AGC <500 cells/mm^3	Platelet count <50,000 cells/mm^3	AGC	(Day)	Platelets × 10^3	(day)
0.8	8	14	2	0	0	1.9	(21)	228	(13)
1.0	7	17	1	1	0	2.0	(21)	187	(13)
1.2	6	13	3	2	0	1.3	(22)	207	(14)
1.5	9	14	2	3	1	1.1	(21)	196	(13)
1.75	7	9	2	4	–	0.3	(22)	132	(14)
2.0	5	6	0	4	0	0.1	(18)	100	(14)

AGC, absolute granulocyte count

Table 3. Nonhematologic toxicity

Dose (mg m^{-2} h^{-1})	Patients	Courses	Toxicity grade	Nausea/vomiting	Diarrhea[a]	Headache	Malaise
0.8	8	14	1	1	0	0	0
			2	2	0	0	0
1.0	7	17	1	1	0	1	0
			2	2	0	0	0
1.2	6	13	1	3	1	2	0
			2	2	0	1	0
1.5	9	14	1	4	0	2	1
			2	1	0	1	0
1.75	7	9	1	2	0	1	0
			2	1	0	1	0
2.0	5	6	1	2	1	2	0
			2	0	0	0	0

[a] 1 patient treated at the 1.5-mg/m^2 dose level who developed malaise also had grade 3 diarrhea

courses. Four patients who received an initial dose of 2.0 or 1.75 mg m^{-2} h^{-1} required subsequent dose reduction.

A summary of the hematologic toxicity data from the last six dose escalations is presented in Table 2. The dose-limiting toxicity was myelosuppression characterized by delayed granulocytopenia along with relative sparing of platelets. Maximal granulocytopenia was documented on day 21, with recovery being noted in the majority of patients by day 28. Nadir granulocyte values of less than 500 cells/mm^3 were observed in 2 of 6 patients treated at 1.2 mg m^{-2} h^{-1}, 3 of 9 subjects treated at 1.5 mg m^{-2} h^{-1}, in 4 of 7 individuals treated at 1.75 mg m^{-2} h^{-1}, and in 4 of 5 patients treated at 2.0 mg m^{-2} h^{-1}; Cumulative myelosuppression was not observed in the small number of patients treated at each level.

Nonhematologic toxicities, including nausea, vomiting, diarrhea, headache, and malaise, were mild and did not appear to be dose-dependent. The incidence of nonhematologic toxicity resulting from the last six dose escalations is shown in Table 3. The amount of DMSO infused within 72 h produced no toxic effects except a bitter taste and generated a strong, garlic-like odor.

Response

No objective complete or partial responses was documented. Three patients experienced prolonged stabilization of their disease: one with clorectal cancer, for ten courses; one with sarcoma, for five courses; and one with non-small-cell lung cancer, for four courses.

Discussion

This study describes our initial clinical experience with the novel antimetabolite fazarabine. Consistent with the preclinical data, myelosuppression was the dose-limiting toxicity. The predominant effect noted was delayed granulocytopenia, with the median nadir occurring on day 21. None of nonhematologic toxicities encountered necessitated a dose reduction. Antineoplastic activity was not observed in any patient, although three subjects with advanced solid tumors had stable disease for a prolonged period. The co-infused DMSO was excreted in the breath, resulting in a bitter taste and a foul odor. Patients were treated in a private room with adequate ventilation. We tried a number of interventions in an attempt to overcome this odor; the most successful was Airkem Neutros-198 (Airwick Industries, Carlstadt, N. J.).

In a corresponding clinical pharmacology study by Ho et al. [8], a radioimmunoassay was developed to measure plasma drug levels. Following the infusion, plasma levels declined triphasically, showing a terminal half-life of 5.1 ± 1.2 h. The area under the plasma drug concentration versus time curve was dose-related. The rate of total clear-

ance was rapid and showed no dose dependence. Plasma steady-state drug levels were achieved within 2–4 h and were dose-dependent [8]. Extrapolating from the relationship between the dose and the steady-state plasma drug level, we surmise that a dose of 1.75 mg m^{-2} h^{-1} would result in a fazarabine concentration range sufficient to inhibit malignant cell growth. This dose is recommended for phase II trials.

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