Phase I and Pharmacological Trial of Fazarabine (Ara-AC) with Granulocyte Colony-stimulating Factor

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ABSTRACT

Fazarabine (1-β-D-arabinofuranosyl-5-aza-cytosine, or Ara-AC) is a nucleoside analogue that consists of the arabinoside ring of 1-β-D-arabinofuranosylcytosine and the pyrimidine base of 5-azacytidine. In Phase I and Phase II trials, neutropenia was dose limiting, with minimal nonhematological toxicity. The in vitro cytotoxic concentrations of Ara-AC could not be achieved in these studies; neutropenia precluded dose escalation. The objectives of this study were: to determine either the maximum tolerated dose of Ara-AC or to safely achieve target plasma levels of 2–5 μg/ml when Ara-AC was administered as a 24-h infusion with granulocyte colony-stimulating factor (G-CSF) to patients with advanced refractory malignancies; to characterize the pharmacokinetic behavior of Ara-AC with G-CSF; and to define the relationship of Ara-AC pharmacokinetics to toxicity. Twenty-four patients received 67 courses of Ara-AC at doses of 54–112 mg/m²/h. Dose-limiting toxicity was approached but not reached. Grade 3 or 4 neutropenia and nausea were the principle side effects. Steady-state plasma concentrations exceeded the minimum target concentration of 2 μg/ml in all patients who received ≥78 mg/m²/h for 24 h. The maximum target concentration was approached during administration of 112 mg/m²/h for 24 h. The mean steady-state clearance was 475 ± 103 ml/min/m² and did not change with dose. One partial response was seen. One patient received 16 courses and another received 7 courses of therapy before progression.

Ara-AC can be safely administered in doses that result in plasma concentrations of 2–5 μg/ml if it is given with G-CSF. Phase II trials of Ara-AC in selected malignancies are planned.

INTRODUCTION

Fazarabine (Ara-AC); Fig. 1) is an analogue of both Ara-C and 5-AC that was synthesized by Beisler et al. (1,2) at the National Cancer Institute in the late 1970s. Ara-AC and Ara-C differ from 5-AC by the stereochemical inversion of the hydroxyl group at the 2’ position of the molecule (Fig. 1). Ara-AC and 5-AC differ from Ara-C by triazine rings, resulting from the substitution of a nitrogen for the carbon-5 in the pyrimidine base of Ara-C.

Ara-AC is unstable in aqueous media, where it undergoes hydrolysis. The drug gains access to the cytoplasm via a nucleoside transport mechanism (3). It is initially phosphorylated by deoxycytidine kinase (the rate-limiting anabolic enzyme) to the monophosphate form and is subsequently phosphorylated to the di- and triphosphate forms (Ara-ACTP; Ref. 4). Unlike Ara-C, Ara-AC is resistant to deamination by cytosine deaminase (5). This resistance could represent a potential therapeutic advantage for Ara-AC over Ara-C and 5-AC.

Preclinical activity of Ara-AC was observed in a subline of L1210 murine leukemia cells that are resistant to 5-fluourouracil (6,7). Additionally, Ara-AC showed tumoricidal activity in a P-388 murine cell line that is resistant to doxorubicin, vincristine, melphalan, and methotrexate (8). Antitumor activity was observed in human tumor xenografts, including CX-1 colon cancer, LX-1 lung cancer, and MX-1 mammary carcinoma. In contrast to the growth inhibition that is observed when CX-1 and LX-1 cell lines are exposed to Ara-AC, both cell lines are resistant to 5-AC and Ara-C. Also, Ara-AC exhibited inhibitory activity in 11 of 18 other human tumor xenografts, including leukemia, lung, breast, colon, ovarian, melanoma, and medulloblastoma cell lines. Ara-C exhibited activity in six of these cell lines (9). These findings suggest that Ara-AC possesses a broader spectrum of activity than does Ara-C.

On the basis of the favorable xenograft activity, the mechanisms of action were elucidated. Ara-ACTP is incorporated into DNA, decreasing the rate of DNA synthesis (10). The drug also acts as a fraudulent nucleotide substrate for both RNA and DNA polymerase.

1 The abbreviations used are: Ara-AC, 1-β-D-arabinofuranosyl-5-aza-cytosine; Ara-C, 1-β-D-arabinofuranosylcytosine; 5-AC, 5-azacytidine; C<sub>ss</sub>, steady-state plasma concentration; G-CSF, granulocyte colony-stimulating factor; HPLC, high-performance liquid chromatography; DAC, 2’-deoxy-5-azacytidine; C<sub>cl</sub>, steady-state clearance; QA, quality assurance; Ara-ACTP, 1-β-D-arabinofuranosyl-5-aza-cytosine triphosphate.

Received 3/21/97; revised 8/20/97; accepted 8/25/97.

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1 This work was supported by NIH Grant MO1-RR00585, National Cancer Institute Grant U01 CA69912-01, and NIH Grant CA15083 and a grant from the Mayo Foundation for Research and Education. This work was presented in part at the 87th Annual Meeting of the American Association for Cancer Research, held April 20–24, 1996, in Washington, DC, and at the Fall 1996 National Cancer Institute Phase I Meeting, held September 17–18, 1996, in Bethesda, MD.

2 To whom requests for reprints should be addressed. Phone: (507) 284-4430; Fax: (507) 284-1803.
DNA polymerase. Finally, Ara-AC induces hypomethylation of cytosine bases in newly replicated DNA strands. This effect causes both abnormal gene activation and altered phenotype in model tumor systems (11).

Preclinical toxicological and scheduling studies indicated that Ara-AC toxicity is dependent on dose rate, the duration of exposure, and total dose but is not related to peak plasma concentration (4, 6, 7, 9). In L1210 leukemia-bearing mice, a 24-h continuous infusion schedule was superior to an every-3-h bolus injection schedule, given four times within a 24-h period (7).

Several schedules were evaluated in early Phase I trials, including a bolus schedule for five consecutive days, a 24-h infusion schedule, and a 72-h infusion schedule. Phase II studies were then conducted in a number of tumor types (see "Discussion"). Steady-state plasma concentrations of greater than 2 \( \mu g/ml \) were associated with a greater cell kill in studies that were done in mice bearing L1210 leukemia (7, 8). Cytotoxicity close to the lower limit of this range were achieved using the 24-h schedule of Ara-AC. Because the dose-limiting toxicity of Ara-AC in all Phase I and II studies was leukopenia, the potential for escalating Ara-AC doses to the target plasma level of 2-5 \( \mu g/ml \) existed only with the use of the cytokine G-CSF.

This study was designed to assess the feasibility of administering escalating doses of Ara-AC as a 24-h infusion with G-CSF support until a target plasma steady-state drug level of 2-5 \( \mu g/ml \) was achieved or dose-limiting toxicity was encountered. Other objectives were to characterize the toxicities associated with Ara-AC and G-CSF administered on this schedule and to describe the pharmacological behavior of Ara-AC given on this schedule.

PATIENTS AND METHODS

Patient Eligibility. Patients selected for this study had a histologically confirmed malignancy for which no potentially curative therapy or no therapy with greater potential benefit than that of Ara-AC was available. Eligibility criteria included: age of \( \geq 18 \) years; an Eastern Cooperative Oncology Group performance score of \( \leq 2 \); sustained intake of \( \geq 1200 \) calories per day; adequate hematological (absolute neutrophil counts of \( \geq 1500 \) cells/\( \mu l \) and platelet counts of \( \geq 130,000 \) cells/\( \mu l \)), renal (creatinine of \( \leq 1.3 \) mg/dl), and hepatic (bilirubin of \( \leq 1.1 \) mg/dl) functions; two or fewer prior chemotherapy regimens, not including mitomycin-C; absence of central nervous system metastases or severe coexisting morbid disease, such as heart disease, precluding full compliance with the study; and ability to understand and sign an informed consent document.

Dosage and Administration. The starting dose of Ara-AC was 54 \( \mu g/m^2/\)h, infused over 24 h every 28 days. Three patients were treated at 54 \( \mu g/m^2/\)h without G-CSF. Three additional patients were treated at 54 \( \mu g/m^2/\)h with G-CSF given at a dose of 5 \( \mu g/kg/\)day, starting on day 3 and continuing until the absolute neutrophil count exceeded 10,000 cells/\( \mu l \). All patients entered subsequently received G-CSF as part of their treatment. Subsequent dose escalations were 65, 78, 94, and 112 \( \mu g/m^2/\)h. At least three patients were entered at each dose level. If a single episode of dose-limiting toxicity was seen, an additional three patients were to be accrued at that dose level. Dose-limiting toxicity was defined as grade 3 nonmyeloid toxicity, excluding myalgias or subjective-type symptoms such as fatigue and lethargy. Hematological parameters defining the maximum tolerated dose were an absolute neutrophil count of <500 cells/\( \mu l \) for \( >5 \) days or a platelet count of <25,000 cells/\( \mu l \) for \( >5 \) days. Any grade 5 toxicity was considered to be dose limiting. The maximum tolerated dose was defined as the dose below which dose-limiting toxicity was seen in two or more of six patients.

Ara-AC was supplied by the Drug Synthesis Branch, Division of Cancer Treatment, National Cancer Institute (Bethesda, MD), as a 250-\( \mu g \) vial containing a lyophilized white powder. Reconstitution was done with 3.5 ml of sterile 70% (v/v) DMSO to yield a 70 \( \mu g/ml \) solution. Ara-AC is unstable in aqueous medium and in plasma due to the lability of the triazine ring. This stability was known to be improved in DMSO, which was therefore used as the injection vehicle. Ara-AC, dissolved in DMSO, was administered via a syringe pump through a polyolefin line and piggy-backed on the side port of an i.v. of 5% dextrose and water running at 150 ml/h.

Follow-Up Studies. Histories, physical examination, albumin, alkaline phosphatase, aspartate aminotransferase, total and direct bilirubin, and creatinine were performed at baseline and, at least, monthly. Complete blood counts and differential counts were performed at baseline and weekly, except when the absolute neutrophil count was <1000 cells/\( ml \), in which case complete blood counts were done daily. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (12). Tumors were evaluated or measured after every two cycles, unless clinical factors indicated the need for earlier evaluation.

Complete response required disappearance of all tumor that was initially observed, with no evidence of new areas of malignant disease. A partial response required a >50% reduction in the sum of the products of the longest perpendicular diameters of all measurable indicator lesions, with no new lesions appearing. Stable disease required no new lesions and no increase in the sums of the products of the longest perpendicular diameters of measurable indicator lesions by \( \leq 50% \). Progressive disease was the development of new malignant disease or an increase in the sums of the products of the longest perpendicular diameters of measurable indicator lesions by \( >50% \).

Specimen Collection. Blood samples (7 ml) were collected in heparinized tubes and immediately chilled in an ice-water bath for 1 min, and plasma was separated by centrifug-
The variation between days of the three QA samples were 14, 5.

Cs 7%.

0.08-8.0 p.g/ml, with coefficients of variation of the slope of Ara-AC and DAC were 100%. The sensitivity limit for Ara-AC QA samples with concentrations of 0.16, 1.6, and 4 p.g/ml were centrifuge tube and stored on ice until ready for HPLC analysis. Analyzed with the standard curve and patient plasma specimens.

Filtration (1100 × g for 3 min) in a refrigerated centrifuge (4°C). Aliquots (1 ml) of plasma were transferred into cryogenic tubes, capped, and immediately frozen. Specimens were stored at −70°C until HPLC analysis. Blood samples were drawn prior to drug infusion and at 2, 4, 6, 22, and 24 h during the fazarabine infusion.

**Sample Preparation and Analysis.** Fazarabine (NSC 614629) and DAC were supplied by the Drug Synthesis Branch, Division of Cancer Treatment, National Cancer Institute (Bethesda, MD). HPLC-grade solvents were obtained from commercial sources, and all other reagents were the highest grade available and were used as received. The HPLC plasma assay was based on a procedure published by Heideman et al. (13). Separations were achieved by a column-switching technique, in which an Apex I. octadecyl precolumn (3 cm × 4.6 mm, inside diameter of 5 μm; Jones Chromatography, Littleton, CO) was installed in a 10-port Valco switching valve in place of a sample loop and an Apex I. octadecyl analytical column (25 cm × 4.6 mm, inside diameter of 5 μm) was installed between the switching valve solvent exit port and the UV absorbance detector. The HPLC columns were washed with 0.1 m citric acid/0.2 m sodium phosphate (pH 2.6) prior to analysis of each set of patient samples. The mobile phase consisted of 1% acetonitrile in 10 mm potassium phosphate buffer (pH 6.8). The flow rate, injection volume, and UV absorbance wavelength were 1 ml/min, 50 μl, and 240 nm, respectively.

To prepare plasma samples for HPLC analysis, plasma (0.5 ml) containing 0.5 μg of DAC was added to a phenylboronic acid column that had been washed with 1 ml of methanol and 1 ml of 10 mm potassium phosphate (pH 8.0) just prior to use. The eluant was collected by centrifugation in a fixed angle rotor (110 × g for 3 min) at 4°C. Following elution of the column with 0.5 ml of 10 mm potassium phosphate (pH 4) via centrifugation at 110 × g for 3 min, the combined supernatant was placed in an Amicon micropartition system, and filtrate was collected by centrifugation at 1580 × g in a fixed-angle rotor for 15 min at 4°C. The filtrate was then transferred to a silenced centrifuge tube and stored on ice until ready for HPLC analysis. QA samples with concentrations of 0.16, 1.6, and 4 μg/ml were analyzed with the standard curve and patient plasma specimens. The variation between days of the three QA samples were 14, 5, and 6%, respectively. Using 0.5 ml of plasma, the recoveries of Ara-AC and DAC were 100%. The sensitivity limit for Ara-AC was 0.08 μg/ml, and standard curves were linear over the range 0.08–8.0 μg/ml, with coefficients of variation of the slope of 7%. Cs was determined as the mean of the concentration values that were determined 22 and 24 h after the beginning of drug administration. CI, was determined according to the equation $C_{\text{in}} = k_0/C_{\text{ss}}$, where $k_0$ is the Ara-AC infusion rate.

### RESULTS

**Patient Characteristics.** Twenty-four adult Caucasian patients, 8 women and 16 men, with histological confirmation of malignancy were entered into the study. Patient age ranged from 38 to 73 years, with a median age of 58 years. Twenty-one patients had gastrointestinal primary sites, including 15 colon cancer, 1 duodenal cancer, 1 biliary tract cancer, 1 primary hepatoma, 1 pancreatic cancer, and 2 gastric cancers. One patient had melanoma, one patient had a sarcoma in the connective tissues of the shoulder, and one patient had a head and neck primary cancer in the nasal cavity. All patients entered had received no, one, or two prior chemotherapy regimens. The median number of prior regimens was one. No patient had received prior radiation to >25% of bone marrow volume. A total of 67 treatments were administered to patients. Ten patients received 1 cycle, 6 received 2 cycles, 3 received 3 cycles, 2 received 4 cycles, 1 received 5 cycles, 1 received 7 cycles, and 1 patient received 16 cycles of therapy. The median number of cycles per patient was two.

Three patients were entered at each dosage level, with six patients each entered at both 65-mg/m²/h plus G-CSF and 112-mg/m²/h plus G-CSF dose levels. At 65 mg/m²/h, an episode of diminished renal function was noted that subsequently proved to be due to ureteral obstruction. Because this was initially felt to be possibly drug related, the cohort treated at that level was expanded to six patients. However, the dose escalation was continued once it became clear that this decline in renal function did not appear to be a treatment-related toxicity. The pharmacological goal of Cs of 2–5 μg/ml had been attained for all patients treated at a dose level exceeding the 65-mg/m²/h dose. The variations between days of the QA samples in the three concentrations noted above were 14, 5, and 6%, respectively.

**Toxicity.** The predominant toxicity was hematological. Table 1 depicts the absolute neutrophil count nadir during the first cycle of treatment by dose for all patients. The platelet nadir was more clearly linked to dose than it was to the absolute neutrophil count nadir. Fig. 2 displays the interval blood count values for WBCs (Fig. 2A) and platelets (Fig. 2B) over the first cycle of treatment. The WBC values uniformly indicated the nadir to occur by day 8–10 after treatment for all dose levels.

### Table 1

<table>
<thead>
<tr>
<th>Dose (mg/m²/h)</th>
<th>No. of patients</th>
<th>ANC (cells/mm³)</th>
<th>Platelet count, × 10⁵, (cells/mm³)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Median</td>
<td>Range</td>
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<tr>
<td>54, no G-CSF</td>
<td>3</td>
<td>224</td>
<td>176–399</td>
</tr>
<tr>
<td>54, + G-CSF</td>
<td>3</td>
<td>592</td>
<td>507–1240</td>
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<tr>
<td>65</td>
<td>6</td>
<td>1718</td>
<td>180–7245</td>
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<tr>
<td>78</td>
<td>3</td>
<td>1240</td>
<td>336–1792</td>
</tr>
<tr>
<td>94</td>
<td>3</td>
<td>1160</td>
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</tr>
<tr>
<td>112</td>
<td>6</td>
<td>477</td>
<td>80–1568</td>
</tr>
</tbody>
</table>

*ANC, absolute neutrophil count.

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Toxicity. The predominant toxicity was hematological. Table 1 depicts the absolute neutrophil count nadir during the first cycle of treatment by dose for all patients. The platelet nadir was more clearly linked to dose than it was to the absolute neutrophil count nadir. Fig. 2 displays the interval blood count values for WBCs (Fig. 2A) and platelets (Fig. 2B) over the first cycle of treatment. The WBC values uniformly indicated the nadir to occur by day 8–10 after treatment for all dose levels.
The horizontal dotted lines in Fig. 2A indicate that grade 3 and grade 4 toxicity levels were rarely seen, with eight incidences of WBC counts of <1900 cells/mm² observed. A comparison was made regarding the time to recovery of neutrophil counts for the patients treated with and those treated without G-CSF at the 54-mg/m² dose. The time to recovery of the neutrophil count to normal was approximately half as long in patients treated with G-CSF compared to patients who received no G-CSF. In addition, we found no relationship between the dose of Ara-AC and the number of doses of G-CSF required for an absolute neutrophil count that exceeded 10,000 cells/µl to recover, among those patients who received G-CSF. Platelets counts moved with remarkable homogeneity to minimum values at approximately day 10 after treatment for all dose levels (Fig. 2B). Grade 3 and 4 toxicity levels were observed briefly in a few patients. Five episodes were documented when platelet counts declined below 25,000. Recovery from hematological nadirs occurred quickly.

We investigated the relationship between drug concentration and clearance levels with hematological toxicity measures. There was no relationship between clearance and concentration levels with the percentage change of WBCs from baseline through the first cycle (Spearman's ρ correlation coefficients of −0.03 and −0.05 with Ps of 0.9 and 0.8, respectively). The relationship between the percentage change in platelet counts with clearance and concentration was strong (Spearman's ρ correlation coefficients 0.6 and −0.7 with Ps of 0.0007 and 0.0001, respectively). The drop in platelet counts were dose dependent; higher doses were associated with greater drops in platelet count.

Nonhematological toxicity was minor (Fig. 3). No grade 4
or 5 toxicity was noted. Grade 3 myalgia was seen in three patients, grade 3 lethargy was seen in one patient, and grade 3 nausea was seen in one patient. Because the myalgia was felt to be a consequence of G-CSF administration, it was not considered to be a dose-limiting toxicity. The nausea resolved promptly with the use of granisetron and, therefore, was not considered to be a dose-limiting toxicity. Finally, lethargy was felt to be a subjective enough symptom that it was not considered to be a dose-limiting toxicity. The remainder of the most commonly seen toxicities were anorexia, fever, and vomiting. All of these were grade 2 or less. There were no clear relationships between dose level and toxicity, although anorexia, nausea, and vomiting were observed most frequently at the highest dosage level of 112 mg/m²/h.

Subsequent investigation of a dose level-toxicity relationship was carried out by means of Spearman and Kendall correlation coefficients. Relationships were investigated between the number of toxicity episodes of a grade of ≥3 and number of hematological and nonhematological toxicities with the dose level, drug clearance, and drug concentration values (14). None of the correlation coefficients exceeded 0.16 (indicative of near independence), and all were statistically nonsignificant, with associated Ps in excess of 0.45 for the sample of 24 patients. All correlation results were confirmed by inspection of bivariate scatterplots. Hence, there was no evidence to suggest a relationship between the incidence or severity of toxicities and the dose of Ara-AC administered.

**Antitumor Efficacy.** One patient who had failed 5-fluorouracil and leucovorin treatment for metastatic colon cancer and who was treated at the 112 mg/m²/h dose level had a partial regression of pulmonary metastases sustained for 7 months. Thirteen patients had stable disease, including one patient who received 16 cycles of therapy. The remainder of patients had progressive disease. The median time to progression was 62 days from study entry.

**Pharmacokinetics.** Under physiological conditions, the triazine ring of Ara-AC is rapidly hydrolyzed, resulting in an open-ring, nontoxic form of the drug. This reaction is reversible, and the open-ring form can nearly regenerate the parent drug. As a result, both Ara-AC and the open-ring hydrolysis product are present in patient plasma following an i.v. dose of Ara-AC.

Accurate determination of Ara-AC plasma concentrations required rapid sample processing to prevent loss of Ara-AC from plasma prior to analysis. Because previous studies found that the poor stability of Ara-AC may impact upon determination of plasma levels following storage of frozen plasma samples, we evaluated short-term storage of plasma during a seven day period at −70°C and long-term storage by monitoring concentrations in the QA samples. During the clinical trial,
Ara-AC was stable during storage of QA samples (0.16, 1.6, and 4 μg/ml) at −70°C for up to 10 months. On the basis of these results, plasma samples were stored at −70°C and analyzed within 7 days during the early portion of the trial and within 4 weeks during the later portion of the trial.

The steady-state pharmacokinetics of Ara-AC were characterized in all patients. Following administration of 54 mg/m²/h Ara-AC, the mean steady-state Ara-AC concentration was 1.7 μg/ml overall (0.29 μg/m² SD). The lower limit of the target concentration range (2–5 μg/ml) was achieved in five of six patients treated with 65 mg/m²/h Ara-AC (Fig. 4A). The value of C∞ increased in proportion to dose over the >2-fold dose increase during the study. The upper limit of the target concentration range was exceeded in one of six patients treated with 112 mg/m²/h Ara-AC (mean of 4.78 mg/m²; 0.73 mg/m² SD).

The mean overall Clₘ was 517 ml/min/m² during administration of 54 mg/m²/h Ara-AC (Fig. 4B). The value was moderately lower (mean of 399 ml/min/m²; 63 mg/m² SD) following administration of 112 mg/m²/h Ara-AC. Thus, the Clₘ for all patients was 475 ± 103 ml/min/m².

DISCUSSION

Several Ara-AC administration schedules were evaluated in early Phase I trials, including a bolus schedule for 5 consecutive days, a 24-h infusion schedule, and a 72-h infusion schedule. Phase II studies were conducted in a number of tumor types. Bailey et al. (15) reported that the maximum tolerated dose was 54 mg/m²/h, with neutropenia, nausea, and vomiting as dose-limiting toxicities, when 24 patients were treated on a 24-h

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**Fig. 4** A, scatterplot of per-patient Ara-AC Cₙ₀ versus dose level. Target concentration of 2 μg/ml is indicated by a solid line. B, scatterplot of per-patient Ara-AC Clₘ versus dose level.
effects were nausea and vomiting, which were responsive to antiemetics, and fatigue. This favorable nonhematological toxicity profile is largely responsible for the ability to escalate the dose to more than double the maximum tolerated dose that was noted when G-CSF was not used.

Due to the poor plasma stability of Ara-AC reported by previous investigators, we evaluated the recovery of Ara-AC during sample preparation and analysis procedures and the stability of Ara-AC during short- and long-term storage at −70°C (7, 28, 29). Our data were similar to those of Ho et al. (29) because QA specimens were stable during a 10-month storage period, but these data differ from those of Heideman et al. (28), who found unacceptable degradation during storage of frozen plasma at −20°C (25, 26). Our finding of improved stability may have been due to storage at −70°C.

Our pharmacokinetic results are similar to those of previous investigators. A mean $C_{ss}$ of 1.7 µg/ml fazarabine was achieved during 24-h infusion of 54 mg/m²/h (12). The mean $C_{ss}$ was similar to the value observed following 24 or 72 h of infusion of Ara-AC (Table 2). The $C_{ss}$s of Ara-AC were linear over the 2-fold dose escalation, although the modest decrease in clearance observed at the highest dose suggests other mechanisms, in addition to acid hydrolysis, may contribute to Ara-AC plasma clearance at lower doses. The target plasma concentration level was attained in all but one patient at doses of 65 mg/m²/h and above. Thus, when Ara-AC infusions were administered with G-CSF, plasma concentrations of Ara-AC in the range of 2–5 µg/ml were achievable.

Here, we confirm that patients can be safely treated with doses of Ara-AC that achieved plasma levels that were associated with tumor responses in murine xenograft models. The pharmacokinetic analysis confirms the finding by Ho et al. (29) that Ara-AC is stable when plasma is stored at −70°C and that the pharmacokinetics of Ara-AC were linear over the 2-fold dose escalation. The response seen in a patient with metastatic colon cancer at the highest dosage level confirms that Ara-AC has clinical activity in patients, as initially noted in the case of a patient with testicular cancer, as reported by Johnston et al. (17).

Phase II studies using this 24-h infusion schedule to determine whether the dose augmentation can result in a meaningful increase in responses to this drug in selected tumor types are planned. Consideration could be given to a Phase I trial of a 48- or 72-h infusional schedule with G-CSF to examine the toxicities and ability to achieve plasma levels associated with murine xenograft model tumor responses for a longer time interval, by administering Ara-AC given in a similar fashion to that commonly used in clinical practice for Ara-C. Substantial dose escalation would be necessary over the doses of 2 mg/m²/h, which were the recommended Phase II doses in the trials of this schedule without G-CSF, cited above, to achieve target drug levels that were associated with murine xenograft tumor responses, such that those levels may well not be attainable, even with cytokine administration. The North Central Cancer Treatment Group will be evaluating a 24-h infusion of Ara-AC plus G-CSF in patients with previously untreated advanced pancreatic cancer.
ACKNOWLEDGMENTS

We acknowledge the indispensable efforts of Tara Thomas, R.N., Nurse Coordinator; Michelle K. Daiss, Protocol Development Coordinator; Debra J. Sprau, Clinical Research Associate; Pamela Atherton-Skaff, Data Analyst; Alex Adeji, M.D., Ph.D., who reviewed the manuscript; the physicians who refer to and manage patients in the Mayo Clinic Phase I program; and the patients who participated in this trial.

REFERENCES

Phase I and pharmacological trial of fazarabine (Ara-AC) with granulocyte colony-stimulating factor.

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