

Phase I Clinical Trial of Fazarabine as a Twenty-four-Hour Continuous Infusion¹

Howard Bailey,² Kendra D. Tutsch, Rhoda Z. Arzoomanian, Mary B. Tombes, Dona Alberti, Joan Bruggink, and George Wilding³

University of Wisconsin Clinical Cancer Center, Madison, Wisconsin 53792 [H. B., K. D. T., R. Z. A., M. B. T., D. A., J. B., G. W.], and William S. Middleton Memorial Veterans Administration Hospital, Madison, Wisconsin 53705 [G. W.]

ABSTRACT

A phase I trial of fazarabine (ara-AC, 1- β -D-arabinofuranosyl-5-azacytosine, NSC 281272) administered as a 24-h continuous infusion was performed in 24 adults with solid tumor malignancies. The majority of patients had received prior marrow-suppressive therapy. Level 7 (54.5 mg/m²/h for 24 h) was the maximum tolerated dose since during 6 evaluable first courses, 2 episodes of grade 4 granulocytopenia and 3 episodes of grade 3 occurred. Moderate thrombocytopenia also occurred at level 7 with 3 episodes of grade 1 and 1 episode of grade 4 thrombocytopenia during 6 first course treatments. Minimal myelosuppression, principally leukopenia, was seen prior to level 7. The nadir WBC through 47 courses had a linear relationship with plasma steady-state concentrations of ara-AC. The only other toxicity noted was moderate nausea/vomiting, which did not appear to be dose related. Plasma steady-state concentrations of ara-AC were reached in all patients within 4–6 h and ranged from 1.1 μ M (11 mg/m²/h for 24 h) to 7.5 μ M (54.5 mg/m²/h for 24 h). The mean total body clearance of ara-AC for 47 courses, levels 1–7, was 592 \pm 147 (SD) ml/min/m² which is similar to prior pharmacokinetic data from the 24-h and 72-h infusion trials of the Pediatric and Medicine Branches, respectively. There were no objective disease responses during the trial. The recommended adult phase II dose for a 24-h infusion of ara-AC is 45–50 mg/m²/h.

INTRODUCTION

ara-AC⁴ is an analogue of ara-C and 5-AC which shares structural features of both: the arabinose sugar of ara-C along with the triazine base of 5-AC. Due to these structural similarities, ara-AC also has many of the same physical and cytochemical properties of these synthetic pyrimidines. ara-AC, similarly to 5-AC, has its triazine ring reduced in aqueous solutions to inactive products, thus requiring it to be dissolved in an organic solvent like DMSO, and it is resistant to deamination by cytidine-deoxycytidine deaminase (1–3). It is the resistance to deamination, which ara-C lacks, that may provide a therapeutic advantage for ara-AC over ara-C. ara-AC and ara-C require intracellular activation through phosphorylation by deoxycytidine kinase to the triphosphate nucleotide level which inhibits DNA synthesis (4). Therefore, similar mechanisms of resistance and cross-resistance exist between ara-AC and ara-C, as shown in preclinical work. P388 murine leukemia cells which have diminished intracellular deoxycytidine kinase are resistant to both (5). Coadministration of deoxycytidine inhibited the anti-leukemic effect of ara-AC on L1210 murine leukemia models (6).

Received 9/17/90; accepted 12/5/90.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

¹ Supported by NIH Contract NO1-CM57735.

² H. B. is a recipient of an American Cancer Society Clinical Oncology Fellowship Award (89–189).

³ Recipient of an American Cancer Society Career Development Award. To whom requests for reprints should be addressed.

⁴ The abbreviations used are: ara-AC, fazarabine (1- β -D-arabinofuranosyl-5-azacytosine, NSC 281272); ara-C, 1- β -D-arabinofuranosylcytosine; 5-AC, 5-azacytidine; DMSO, dimethyl sulfoxide; CI, continuous infusion; NCI, National Cancer Institute; MTD, maximum tolerated dose.

The most notable preclinical data that separate ara-AC from ara-C and 5-AC is the finding of activity against solid tumor models. Preclinical antitumor activity has been demonstrated for ara-AC in a wide spectrum of tumor models; activity was seen against murine solid tumors (B16 melanoma, Lewis lung carcinoma, and M5076 sarcoma) and human tumor xenografts (CX-1 colon, LX-1 lung, MX-1 mammary carcinomas, and TE-671 medulloblastoma) (7–12).

Schedule dependency of ara-AC, like other nucleosides, has been demonstrated (7, 8). ara-AC given s.c. as a CI over 24 to 48 h to mice bearing L1210 leukemia cells was superior in terms of animal survival to bolus i.p. administration every 3 hours for 4 doses (13). The murine and canine data (7) have shown myelosuppression and gastrointestinal damage as the limiting toxicities.

Due to the above preclinical work, a phase I dose escalation trial was undertaken administering ara-AC as a 24-h CI to assess for pharmacokinetics and toxicity data.

MATERIALS AND METHODS

Patient Selection. Individuals with advanced malignancy for whom no standard effective therapy was available, who gave informed consent according to institutional and Food and Drug Administration guidelines, and who had adequate bone marrow (WBC >4,000/mm, platelet count >100,000/mm), renal (serum creatinine \leq 1.5 mg/dl, or creatinine clearance >60 ml/min), hepatic (aspartate aminotransferase \leq 4-fold normal and bilirubin \leq 1.5 mg/dl), and metabolic (normal calcium and electrolytes) functions were eligible. Patients who had an Eastern Cooperative Oncology Group performance status >2, brain metastases, and a life expectancy of <12 weeks and who had received radiation, hormonal, or immunotherapy within 2 weeks or chemotherapy within 4 weeks (6 weeks for nitrosoureas and mitomycin C) were not eligible.

Drug Formulation. ara-AC was supplied by the Investigational Drug Branch, Division of Cancer Treatment, NCI, Bethesda, MD, as a sterile lyophilized powder in 250-mg vials which was reconstituted with 3.5 ml of sterile 70% DMSO (supplied by NCI) to yield a 70-mg/ml solution. The 24-h dose of ara-AC was divided into two equal syringes (Monoject-BD; Becton Dickinson and Co., Rutherford, NJ), each given over 12 h affixed to a small volume infusion pump (Autosyringe AS20S; Travenol Laboratories, Inc., Hookset, NH). The ara-AC solution was delivered via polyolefin-lined tubing supplied by the NCI (see Refs. 14 and 15) into the side injection port of a peripheral or central i.v. of 5% dextrose in water at a pump-controlled rate of 150 ml/h.

Drug Administration and Dose Escalation. The ara-AC was administered as a 24-h CI every 3 weeks provided preceding toxicity had resolved. Patients received from one to four cycles depending upon disease status, unless there was evidence of a response, in which case they received >4 cycles.

The ara-AC escalation scheme followed is shown in Table 1. The starting dose was selected based upon canine 24-h CI toxicity data which revealed a tolerable dose of 108 mg/m²/h (7) and the initial toxicity data of the Pediatric Branch 24-h CI trial where 20 mg/m²/h produced reversible myelosuppression. Due to presumed intraspecies differences in deoxycytidine kinase levels possibly contributing to greater toxicity in humans (7) and possible greater tolerance of myelosuppression in pediatric patients compared to adults, it was reasoned

Table 1 Dose escalation scheme

Level	Dose (mg/m ² /h for 24 h)	Patients entered on study	Prior chemotherapy and/or radiation therapy	Evaluable courses
1	11.0	3	3	8
2	14.3	3	1	8
3	18.6	3	2	7
4	24.2	3	2	8
5	31.5	3	3	7
6	41.0	3	1	6
7	54.5	9	8	9

that <15 mg/m²/h for 24 h should be a safe starting dose. A minimum of 3 patients were treated and evaluated for ≥3 weeks at each level; if ≥grade 3 myelosuppression, ≥grade 2 mucositis, or ≥grade 3 vomiting occurred in 2 patients or any other nonhematological toxicity was noted, a total of 6 patients were entered at that dose level. If no unacceptable toxicity was noted, the next 3 patients were entered at the next higher level. Any patient having grade 4 granulocytopenia or grade 3 or 4 thrombocytopenia received subsequent cycles at the next lower level of ara-AC.

The MTD was defined as that dose level in which grade 2 mucosal or grade 3 nonmucosal toxicity occurs in more than one-third of the patients. If grade 4 toxicity occurs in more than one-third of the patients at a dose level, then the MTD would be the next lower dose level. The NCI Common Toxicity criteria was used to grade all toxicity during the trial.

Hematological and nonhematological parameters were monitored weekly.

Pharmacokinetic Methods. Heparinized blood samples were obtained prior to treatment (assay blank) and at 2, 4, 6, 22, and 24 h into the ara-AC infusion. To minimize hydrolytic degradation of ara-AC, blood samples were immediately placed on ice and the plasma was separated as soon as possible by centrifugation at 1000 × g in a refrigerated centrifuge (5°C). Plasma samples were placed on ice and assayed for ara-AC within 2 h of being drawn, using the high-performance liquid chromatographic method of Heidemann *et al.* (16). Pure ara-AC for assay standards was supplied by Dr. Karl Flora of the NCI Pharmaceutical Resources Branch. Samples were kept on ice during all assay preparation steps. For each course the steady-state plasma concentration (C_{ss}) was determined as the mean of the 22- and 24-h samples. The apparent total body clearance (Cl_{tb}) of ara-AC was calculated as infusion rate/C_{ss}.

RESULTS

Twenty-seven patients (24 evaluable) were entered on this trial and received 53 evaluable courses. Two patients entered on study were unevaluable due to urgent radiotherapy starting on days 12 and 13 of course 1 for symptoms related to progressive disease, and one patient was unevaluable after the course 1 infusion was stopped after three h due to signs of an underlying bacteremia. Patient characteristics are listed in Table 2. The majority of patients had received prior chemotherapy or radiation therapy which were fairly evenly distributed between levels (see Table 1).

Pharmacokinetics. Steady-state plasma concentrations of ara-AC were reached in all patients within 4–6 h of the initiation of the infusion. The pharmacokinetic data are summarized in Table 3. Over the dose range studied, 11.0 to 54.5 mg/m²/h, ara-AC exhibited linear pharmacokinetics. C_{ss} increased linearly with dose (r = 0.960, P < 0.001), as shown in Fig. 1. Clearance did not vary with dose. Thirteen patients received two or more courses of ara-AC. There was no significant difference in the Cl_{tb} for the last course as compared with the first course in each patient (P = 0.52 by paired t test). The mean clearance for 47 courses of ara-AC over the dose range

Table 2 Patient characteristics

No. of patients entered	27
No. of patients evaluable	24
Age (yr)	
Median	60
Range	29–75
Males/females	21/6
No. of patients with prior therapy	
Chemotherapy	8
Chemotherapy + radiation therapy	7
Radiation therapy	5
Biological response modifier only	2
No prior chemotherapy or radiation therapy	5
Performance status (Eastern Cooperative Oncology Group)	
0	6
1	19
2	2
Diagnosis	
Non-small cell lung	7
Colon	6
Renal cell	3
Melanoma	2
Gastric	2
Unknown	2
Noncolon gastrointestinal	2
Thyroid	1
Sarcoma	1

Table 3 ara-AC pharmacokinetic parameters

Dose (mg/m ² /h)	No. of patients (no. of courses)	C _{ss} ^a (ng/ml)	Cl _{tb} (ml/min/m ²)
11.0	3 (7)	276 ± 95 ^b	738 ± 263
14.3	4 (9)	412 ± 61	588 ± 85
18.6	3 (7)	581 ± 117	550 ± 105
24.2	3 (7)	660 ± 138	658 ± 137
31.5	3 (6)	1,011 ± 70	521 ± 38
41.0	4 (4)	1,216 ± 247	579 ± 112
54.5	7 (7)	1,817 ± 359	516 ± 95

^a C_{ss}, plasma steady-state concentration; Cl_{tb}, apparent total body clearance.
^b Mean ± SD.

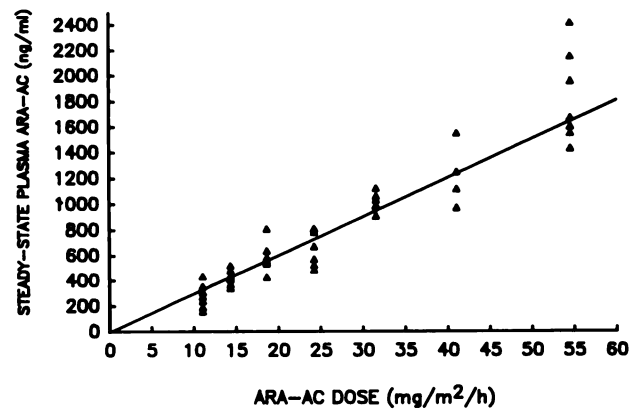


Fig. 1. Steady-state plasma concentrations of ara-AC at the end of the 24-h infusion as a function of dose level (n = 47, r = 0.960, P < 0.001).

studied was 592 ± 147 (SD) ml/min/m². Mean plasma C_{ss} ranged from 276 ng/ml (1.1 μM) at the initial dose level to 1817 ng/ml (7.5 μM) at the MTD, 54.5 mg/m²/h.

Toxicity. Myelosuppression, principally granulocytopenia with occasional thrombocytopenia, was the dose-limiting toxicity of this trial. Level 7 (ara-AC, 54.5 mg/m²/h for 24 h) was the MTD since over 6 evaluable first courses there were 2 episodes of grade 4 granulocytopenia and 3 episodes of grade 3 cytopenia. Level 7 also had moderate thrombocytopenia with 3

episodes of grade 1 and 1 course with grade 4 of 6 evaluable first courses.

The myelosuppression seen during the trial was quite limited until level 7, with one grade 2 granulocytopenia at level 5 (31.5 mg/m²/h for 24 h) and a grade 3 at level 6 (41.0 mg/m²/h for 24 h) being the extent of the granulocytopenia prior to level 7. There were occasional episodes of mild leukopenia throughout levels 1–6 and minimal thrombocytopenia with 2 courses having grade 2 platelet nadir counts and one course with a grade 1 platelet nadir at level 6 (see Table 4). Prior to level 7, the nadir WBC was occurring at days 14 and 15; at level 7, the median time to nadir WBC and nadir granulocyte count was days 15 and 18, respectively. The leukopenia encountered usually recovered by day 21, such that only two courses at level 7, delayed 1 week each, were the extent of the treatment delays during the trial.

The nadir WBC decreased with increasing plasma C_{ss} over the course of this trial, as shown in Fig. 2 for the first course in each patient for whom plasma concentrations were available (n = 25). This relationship was fairly linear (r = 0.632, P < .001). Six patients received 3 or more courses of ara-AC. There was no significant difference in the WBC nadir of the last course when compared with the first course in each patient (P = 0.28 by paired t test).

Three patients had significant platelet count elevations (>1 million cells/mm³) during course 1 (days 21 and 22) without a significant nadir count (99,000–198,000 cells/mm³) preceding it. Two of the patients were at level 6 and did not receive further courses on study. The remaining patient was at level 7 for course 1 but due to a grade 4 granulocytopenia was dose reduced to level 6 for courses 2 and 3 which had no significant platelet abnormalities. Two of the patients' platelet counts returned to normal by day 28, but one of the patients at level 6 did not

have the platelet count return to normal (448,000 cells/mm³) until day 39. The peak occurred on day 24 (1,250,000 cells/mm³) with a gradual decline until day 39. WBC and RBC were stable through the course other than a grade 3 WBC on day 13. Marrow examination on day 32 revealed a hypercellular marrow with granulocytic and megakaryocytic hyperplasia without evidence of cancer.

There were 14 courses with hemoglobin counts that decreased (grades 1–3) on study. Thirteen courses had grade 1–2 transient decreases in the hemoglobin values during the patients' first or second course. One patient (level 1, course 2) had a grade 3 hemoglobin drop which coincided with progression of hepatic and intraabdominal metastases from colon cancer. Eight patients received >2 courses of drug on study with none having significant hemoglobin drops.

The nausea and vomiting encountered during the trial were not frequent, were mild, and were possibly dose related with a slight increased incidence with dose escalation (see Table 4). Twenty-nine courses had a graded toxicity for nausea/vomiting of which 26 were ≤grade 2. Antiemetics were given not on a schedule but on an as needed basis when grade 2 nausea occurred.

Significant subjective fatigue was noted by 3 patients over 4 courses (level 1 + 2), 2 courses with grade 1 and 1 course each with grade 2 + 3. The 3 patients had other courses either preceding or after the above mentioned course, without complaints of fatigue. No further fatigue toxicity was encountered on the study.

A patient at level 2 with course 1 developed a pruritic maculopapular rash on her thorax on days 1 + 2. This resolved without specific treatment and did not recur with course 2. During course 2 an extravasation of ara-AC occurred around a peripheral i.v. site. Ice was applied and the resulting erythema resolved in 2 days.

No hepatic or renal toxicity was seen during the trial. There were no treatment-related deaths on study. There was one hospitalization due to febrile neutropenia and thrombocytopenia in a patient at level 7. No objective responses (partial or complete response) were seen during the trial.

Table 4 Predominant toxicity of evaluable courses

Level	Total courses	No. of courses with grade of toxicity						
		WBC nadir				Nausea/vomiting		
		1	2	3	4	1	2	3
1	8	1	1	2	0	1	1	0
2	8	2	0	0	0	1	2	1
3	7	5	1	1	0	2	0	0
4	8	4	2	0	0	1	3	1
5	7	2	2	1	0	2	4	0
6	6	3	2	1	0	4	1	0
7	9	0	5	3	1	1	3	1

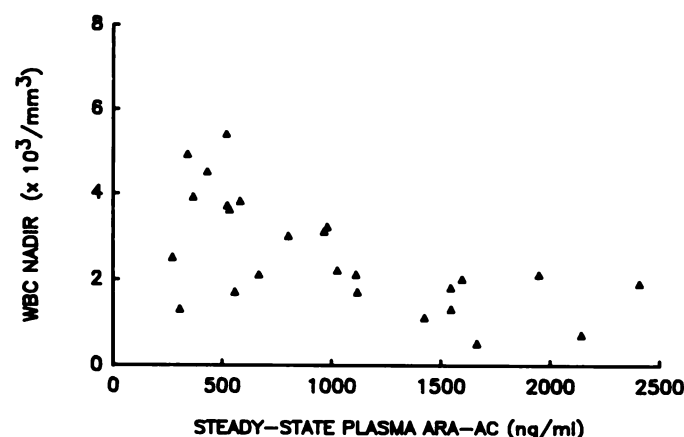


Fig. 2. Nadir WBC as a function of plasma ara-AC concentration for each patient's first course of drug (n = 25, r = -0.632, P < 0.001).

DISCUSSION

This phase I trial had no unexpected toxicity when compared to prior phase I studies with ara-AC (14, 15), with reversible myelosuppression and mild nausea and vomiting being the main toxicities encountered. What was unusual about this trial was the dose at which dose-limiting toxicity was encountered, when compared to the prior work with a 24-h CI schedule. The trial completed by the Pediatric Branch at the NCI on 16 heavily pretreated children determined the MTD as 15 mg/m²/h for 24 h. A possible explanation is the extent of pretreatment. The adult patient population on this trial also had received prior treatment with the majority of patients having had prior cytotoxic chemotherapy and/or radiation therapy albeit not to the presumed extent of the pediatric patients. In reviewing prior treatment by level, only level 6 had minimal pretreatment with cytotoxics (one patient with radiation therapy). This may explain the minimal myelosuppression seen at this level especially compared to level 7 where 8 of 9 patients had prior myelosuppressive therapy. Also the MTD could have easily been level 6 due to unacceptable toxicity at level 7. Two patients entered at level 7 had a complete course of drug but were considered unevaluable for toxicity due to emergent radiation therapy

having been started on days 12 and 13 for severe pain related to bony disease and tumor compression on a peripheral nerve. Both patients had grade 4 granulocytopenia and grades 2 and 3 thrombocytopenia on day 14. If these patients were included in evaluation of level 7, more than one-third of patients would have had unacceptable toxicity, thus defining level 6 as the MTD. Even if level 6 (41.0 mg/m²/h for 24 h) was the MTD, it is still substantially higher than the Pediatric Branch data.

We compared our drug clearance data for a difference in drug clearance in adults *versus* children. However, our results with a mean ara-AC clearance of 592 ± 147 ml/min/m² were quite similar to the mean ara-AC clearance of 571 ml/min/m² at 15 mg/m²/h as reported by the Pediatric Branch trial (14). A study of ara-AC given as a 72-h CI by the Medicine Branch of the NCI (15) reported a similar mean clearance of 647 ± 141 ml/min/m² over a smaller dose range, 1.25–6.94 mg/m²/h. This information does not explain the marked difference in MTD doses but does illustrate the linearity of ara-AC pharmacokinetics over a wide dose range. Another possible explanation of the marked difference in MTD doses could be related to the finding of intraspecies differences in deoxycytidine kinase (7). If children had higher levels of deoxycytidine kinase, it would lead to greater toxicity at lower doses. This seems unlikely, since this possible phenomenon would also affect ara-C metabolism, and no marked difference exists between the tolerable ara-C dose for adults and children. Due to the known schedule dependency of ara-AC (7, 8), it is not valid to compare this trial in terms of dose intensity to the Medicine Branch trial since it was a 72- rather than 24-h CI.

Even though no objective responses were seen during the trial, the increased doses tolerated with corresponding higher C_{50} reached (1.8 µg/ml/7.5 µM) is encouraging, when compared to prior *in vitro* cytotoxicity testing of ara-AC. Exposure of L1210 cells to a 24-h exposure of 1 µg/ml (4.1 µM) ara-AC reduced the cloning efficiency to 7 and 0.2% of control, respectively (13), while exposure of Molt-4 cells (a T-lymphoblast line) to 0.24 µg/ml (1 µM) for 24 h decreased cloning efficiency to 2% of control (17). The human colon carcinoma cell line (HT-29) was exposed to ara-AC for 24 h at 2.4 µg/ml (10 µM) with a resultant cloning efficiency of 3% of control (4).

The toxicity seen during the trial was similar to the prior studies with marked myelosuppression, primarily leukopenia with occasional thrombocytopenia being the predominant dose-related toxicity. There did not appear to be any significant cumulative marrow toxicity from ara-AC over a limited number of courses per patient. The odor associated with the use of DMSO was tolerated and the minimal to moderate nausea/vomiting encountered was also seen in the previous phase I trials. No other significant toxicity was seen, including no evidence of hepatic toxicity, which was seen in the Medicine Branch trial.

The unique activity of ara-AC against solid tumor models *in vitro* in contrast to the other arabinoside nucleosides and the finding of minor clinical responses against solid tumors in the

Medicine Branch trial suggest that phase II testing against solid tumors should be done. An even stronger case for this can be made due to the ability of this trial to obtain plasma steady-state levels substantially higher than required for *in vitro* cytotoxicity. The results of this trial suggest that a phase II dose of 45–50 mg/m²/h for 24 h, with some expected moderate to severe reversible myelosuppression, would be appropriate for adults.

ACKNOWLEDGMENTS

We gratefully acknowledge the following people for their help in completion of this trial and the manuscript: Jane Wegenke for administrative assistance; Barry Storer for statistical advice; and Kathy Edge for manuscript preparation.

REFERENCES

1. Townsend, A., Leclerc, J. M., Dutschman, G., *et al.* Metabolism of 1-β-D-arabinofuranosyl-5-azacytosine and incorporation into DNA of human T-lymphoblastic cells (Molt-4). *Cancer Res.*, 45: 3522–3528, 1985.
2. Mojaverian, P., and Repta, A. J. Development of an intravenous formulation for the unstable investigational cytotoxic nucleosides 5-azacytosine arabinoside (NSC 281272) and 5-azacytidine (NSC 102816). *J. Pharm. Pharmacol.*, 36: 728–733, 1984.
3. Notari, R. E., and DeYoung, J. L. Kinetics and mechanisms of degradation of the antileukemic agent 5-azacytidine in aqueous solutions. *J. Pharm. Sci.*, 64: 1148–1156, 1975.
4. Glazer, R. L., and Knode, M. C. 1-β-Arabinosyl-5-azacytosine: cytotoxic activity and effects on the synthesis and methylation of DNA in human colon carcinoma cells. *Mol. Pharmacol.*, 26: 381–387, 1984.
5. Ahluwalia, G., Cohen, M. B., Kang, G. J., *et al.* Arabinosyl-5-azacytosine: mechanisms of native and acquired resistance. *Cancer Res.*, 16: 4479–4485, 1986.
6. Vesely, J., and Piskala, A. Mechanism of action of 1-β-D-arabinofuranosyl-5-azacytosine and its effects in L1210 mouse leukemia cells. *Neoplasma (Bratisl.)*, 33: 3–10, 1986.
7. Grem, J. L., Shoemaker, D. D., Hoth, D. F., *et al.* Arabinosyl-5-azacytosine: a novel nucleoside entering clinical trials. *Invest. New Drugs*, 5: 315–328, 1987.
8. National Cancer Institute, Division of Cancer Treatment, Clinical Brochure. Fazarabine (Ara-AC), NSC 281272, January 1987.
9. Dalal, M., Plowman, J., Breitman, T. R., *et al.* Arabinofuranosyl-5-azacytosine: antitumor and cytotoxic properties. *Cancer Res.* 46: 831–838, 1986.
10. Driscoll, J. S., John, D. G., and Plowman, J. Comparison of the activity of arabinosyl-5-azacytosine, arabinosyl cytosine, and 5-azacytidine against intracerebrally implanted L1210 leukemia. *Invest. New Drugs* 3: 331–334, 1985.
11. Sheridan, M. A., Nines, R. G., Riblet, S. M., *et al.* Glioma and medulloblastoma xenografts as models for brain tumor drug development. *Proc. Am. Assoc. Cancer Res.*, 27: 385, 1986.
12. Wallace, R. E., Lindh, D., and Durr, E. E. Arabinosyl-5-azacytosine (ara-AC), fazarabine, NSC 281272: activity against human tumor xenografts. *Proc. Am. Assoc. Cancer Res.*, 28: 307, 1987.
13. Zaharko, D. S., and Covey, J. M. Arabinosyl-5-azacytosine: plasma kinetics and therapeutic response (L1210) *in vitro* and *in vivo* in mice. *Invest. New Drugs* 3: 323–329, 1985.
14. Heideman, R. L., Gillespie, A., Ford, H., Reaman, G. H., Balis, F. M., Tan, C., Sato, J., Ettinger, L. J., Packer, R. J., and Pohlack, D. G. Phase I trial and pharmacokinetic evaluation of fazarabine in children. *Cancer Res.* 49: 5213–5216, 1989.
15. Surbone, A., Ford, H., Kelley, J. A., Ben-Baruch, N., Thomas, R. V., Fine, R., and Cowan, K. H. Phase I and pharmacokinetic study of arabinofuranosyl-5-azacytosine (fazarabine, NSC 281272). *Cancer Res.* 50: 1220–1225, 1990.
16. Heideman, R. L., Roth, J. S., Ford, H., Kinnard, R. D., Litterest, C. L., and Kelley, J. A. Reverse phase HPLC determination and murine pharmacokinetics of arabinosyl-5-azacytosine. *J. Liquid Chromatog.*, 12: 1613–1633, 1989.
17. Townsend, A., Leclerc, J. M., Dutschman, G., Cooney, D., and Cheng, Y. C. Metabolism of 1-β-D-arabinofuranosyl-5-azacytosine and incorporation into DNA of human T-lymphoblastic cells (Molt-4). *Cancer Res.*, 45: 3522–3528, 1985.