Pharmacokinetics of Continuous Intravenous and Subcutaneous Infusions of Cytosine Arabinoside

By Howard J. Weinstein, Thomas W. Griffin, Judy Feeney, Harvey J. Cohen, Richard D. Propper, and Stephen E. Sallan

The pharmacokinetics of continuous subcutaneous cytosine arabinoside (ara-C) infusions were compared with continuous intravenous infusions. Steady-state serum ara-C levels and myelosuppression were similar with both routes of administration. CSF/serum ara-C ratios ranged from 0.14 to 0.91 (mean, 0.58). Continuous subcutaneous ara-C infusions were a convenient and reliable alternative to intravenous infusions.

CYTOSINE ARABINOSIDE (ara-C) is one of the single most effective agents in the treatment of acute myelogenous leukemia (AML).1,2 Because of its short half-life after a single intravenous or subcutaneous injection3,4 and its S-phase specificity, prolonged intravenous infusions of ara-C have been administered to patients with AML.5 Continuous intravenous (i.v.) infusions of ara-C have been given by standard drip methods or by portable infusion systems.6 In an attempt to minimize the problems of intravenous access and reduce hospitalization time for patients with AML, we investigated a portable infusion system to deliver continuous subcutaneous ara-C. In this study, we compared the serum and cerebrospinal fluid (CSF) levels of ara-C during continuous intravenous (i.v.) and subcutaneous (s.c.) infusions in patients with leukemia and lymphoma.

MATERIALS AND METHODS

Eight children (five with acute lymphoblastic leukemia, two with acute myelogenous leukemia, and one with diffuse lymphoblastic lymphoma) who were receiving maintenance therapy that included continuous i.v. infusions of ara-C were studied. Informed consent was obtained from all patients or their families. Patients ranged in age from 4 to 14 yr, and all were in bone marrow and central nervous system (CNS) remission at the time of study.

Ara-C Delivery System

Ara-C was administered by a portable battery driven infusion pump (Model AS-3D Autosyringe Inc., Hooksett, N.H.). The pump weighed 11 oz and was fitted with a 5-ml disposable plastic syringe (Bectin and Dickinson Co., Rutherford, N.J.). The pump was calibrated to deliver a volume of 5 ml over a 24-hr period by either calibrated to deliver a volume of 5 ml over a 24-hr period by either intravenous or subcutaneous routes. Intravenous administration of ara-C was facilitated by the "piggy-backing" of standard intravenous tubing to the infusion unit and then to an established intravenous line. Use of a 27-gauge "butterfly" needle or lymphangiogram set allowed for uncomplicated and painless administration of subcutaneous ara-C. Areas of subcutaneous tissue of the anterior abdominal wall or anterior upper leg were utilized as subcutaneous injection sites. The sites were rotated on a daily basis to minimize development of skin irritation and to insure maximum absorption of the drug.

Study Protocol

Five patients received 5-day continuous i.v. infusions of ara-C for their first course of therapy and, 3-4 wk later, received a 5-day continuous s.c. infusion. Three additional patients received either a 5-day continuous i.v. or s.c. infusion of ara-C. Blood (5 ml) was taken at 1, 3, 6, 12, 24, 48, 72, 96, and 120 hr after initiation of the ara-C infusion. Lumbar CSF samples were obtained once or twice during the 5-day infusions. Both blood and CSF samples were collected in tubes containing 50 μg of tetrahydrodridine (supplied by H. B. Wood; Drug Synthesis and the Chemistry Branch of the National Cancer Institute). The blood samples were centrifuged and the serum was separated and stored frozen at –20°C.

Assay

A specific radioimmunoassay method for ara-C, developed by T. Okabayashi and coworkers, was adapted for determination of both the serum and CSF ara-C levels.7 The standard curve was linear over a wide range of ara-C concentrations. The lower limit of sensitivity of this assay is 4 × 10⁻⁸ M ara-C. Routine analyses were carried out in duplicate.

RESULTS

Pharmacologic Data

As shown in Fig. 1, the mean ara-C levels plus or minus the standard error of the mean (SEM) are shown for each of the five patients who received 5-day continuous i.v. infusions followed 3-4 wk later by continuous s.c. infusions of ara-C. During the continuous i.v. infusion, serum ara-C levels reached steady state within 1-3 hr and during the continuous s.c. infusions within 12-24 hr. From 24 to 120 hr after initiation of the infusions, there were no significant differences in ara-C levels when comparing continuous i.v. and s.c. infusions. The nadirs and durations of granulocytopenia and thrombocytopenia with either continuous i.v. or s.c. routes were similar.
Fig. 1. Mean serum levels of ara-C (± SEM) in 5 patients who received continuous infusions of ara-C at 200 mg/sq m/day for 120 hr. Closed circles, continuous i.v.; open circles (shaded area), continuous s.c.

Concomitant CSF and serum ara-C levels are listed in Table 1. CSF samples were obtained during steady state. The CSF/serum ratios ranged from 0.14 to 0.91 with a mean of 0.58, similar to that recorded by Ho and Frei. There were no statistically significant differences between CSF ara-C levels at 24 or 120 hr after initiation of the infusion, nor were there any differences in CSF levels with respect to route of continuous infusion.

The continuous s.c. delivery of ara-C via the portable infusion pump was reliable and comfortable for patients. Only the failure to change the pump battery on two occasions resulted in delays in infusion time. There was minimal, if any, erythema, pain, or swelling at the local subcutaneous injection sites.

**DISCUSSION**

We compared the pharmacokinetics of continuous i.v. and s.c. infusions of ara-C and demonstrated that steady-state serum ara-C levels were similar with both routes of administration. The time to reach a steady-state concentration was longer with the continuous s.c. route. The nadir and duration of myelosuppression were similar with both routes of administration. The portable infusion device described in this report overcame the problems of intravenous access. Subcutaneous infusions can be given on an outpatient basis, thus obviating the necessity and the expense of hospitalization. We have demonstrated the dependability and safety of this system for clinical administration of ara-C, analogous to the use of such portable infusion pumps for the administration of continuous infusions of insulin and deferoxamine. Since our initial studies, we have administered over 200 courses of continuous s.c. ara-C on an outpatient basis without incurring any problems of drug delivery.

We have confirmed the observation of Ho and Frei that ara-C penetrates into the CSF when given as a continuous intravenous infusion. The mean CSF/serum ara-C ratio was 0.58, which was similar to that reported by Ho. There were no significant differences in CSF ara-C levels with respect to route of continuous infusion.

Previous investigations have noted that parenteral injection of ara-C resulted in a decrease in CSF blasts in children with CNS leukemia and reduced the incidence of meningeal relapse in adults with non-Hodgkin's lymphoma. Constant infusions of ara-C should result in greater CSF ara-C concentrations than those achieved after bolus administration and possibly be more effective in the treatment of CNS leukemia and lymphoma. Our own childhood AML data, however, suggested that continuous ara-C infusions at a dose of 200 mg/sq m/day did not provide effective CNS prophylaxis. Recently, patients have been treated with high-dose ara-C (3 g/sq m over 1–3 hr), and they achieved serum and CSF levels of ara-C.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time</th>
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<th>Subcutaneous Infusion</th>
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<tr>
<td></td>
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<td>CSF (M)</td>
<td>Serum (M)</td>
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<tr>
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<td>5.8 x 10^{-7}</td>
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<td></td>
<td>120 hr</td>
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</tr>
<tr>
<td>CC</td>
<td>24 hr</td>
<td>5.0 x 10^{-7}</td>
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<tr>
<td></td>
<td>120 hr</td>
<td>6.4 x 10^{-7}</td>
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<tr>
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CONTINUOUS SC INFUSIONS OF ARA-C

much greater than demonstrated in our experience. It is possible that these higher levels will have a greater therapeutic effect. Future clinical studies will be necessary to test these hypotheses.

ACKNOWLEDGMENT

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REFERENCES

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