CONCISE REPORT

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). Because of its short half-life after a single intravenous or subcutaneous injection and its S-phase specificity, prolonged intravenous infusions of ara-C have been administered to patients with AML. Continuous intravenous (i.v.) infusions of ara-C have been given by standard drip methods or by portable infusion systems. 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 the Harvard Medical School, Boston, Mass. Support in part by Research Grants CA-22719 and CA-17700 from the National Cancer Institute, and by a grant from the Clinical Cancer Education Program.

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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.3 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.

We have confirmed the observation of Ho and Frei3 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.3 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 leukemia12 and reduced the incidence of meningeal relapse in adults with non-Hodgkin’s lymphoma.13 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.14 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>
<th>CSF (M)</th>
<th>Serum (M)</th>
<th>CSF (M)</th>
<th>Serum (M)</th>
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<tbody>
<tr>
<td>DH</td>
<td>24 hr</td>
<td>5.3 x 10^{-7}</td>
<td>5.8 x 10^{-7}</td>
<td>3.2 x 10^{-7}</td>
<td>6.2 x 10^{-7}</td>
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<tr>
<td></td>
<td>120 hr</td>
<td>6.4 x 10^{-7}</td>
<td>5.3 x 10^{-7}</td>
<td>4.8 x 10^{-7}</td>
<td>1.0 x 10^{-4}</td>
</tr>
<tr>
<td>MI</td>
<td>18 hr</td>
<td>2.1 x 10^{-7}</td>
<td>8.2 x 10^{-7}</td>
<td>—</td>
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</tr>
<tr>
<td>JL</td>
<td>24 hr</td>
<td>1.2 x 10^{-8}</td>
<td>2.0 x 10^{-8}</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CC</td>
<td>24 hr</td>
<td>5.0 x 10^{-7}</td>
<td>6.2 x 10^{-7}</td>
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<td>—</td>
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<tr>
<td></td>
<td>120 hr</td>
<td>6.4 x 10^{-7}</td>
<td>9.0 x 10^{-7}</td>
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</tr>
<tr>
<td>CG</td>
<td>24 hr</td>
<td>2.6 x 10^{-7}</td>
<td>&lt;4.0 x 10^{-8}</td>
<td>2.3 x 10^{-7}</td>
<td>9 x 10^{-7}</td>
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<tr>
<td>AW</td>
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<td>—</td>
<td>—</td>
<td>2.2 x 10^{-7}</td>
<td>9.1 x 10^{-7}</td>
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<tr>
<td>DM</td>
<td>92 hr</td>
<td>—</td>
<td>—</td>
<td>3.4 x 10^{-7}</td>
<td>1.3 x 10^{-4}</td>
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</table>
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.

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REFERENCES

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