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Pharmacokinetics of ara-C and ara-U in plasma and CSF after high-dose administration of cytosine arabinoside*

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Summary. Cytosine arabinoside (ara-C) and uracil arabinoside (ara-U) levels were measured in the plasma, cerebrospinal fluid (CSF), and urine of 10 patients exhibiting primary central nervous system lymphoma who received 31 infusions of high-dose ara-C (3 g/m^2) as part of their treatment regimen. Peak plasma and CSF ara-C levels were 10.8 and 1.5 μg/ml, respectively. Ara-C was cleared more rapidly from plasma than from CSF. Ara-U appeared rapidly in both plasma and CSF, reaching a peak that was 10 times higher than the corresponding ara-C concentration (104 and 11.2 μg/ml, respectively). Only 4%–6% of the dose was excreted unchanged in the urine, but 63%–73% of it appeared as ara-U within the first 24 h. The presence of leptomeningeal lymphoma did not affect the CSF level of ara-C or ara-U.

Introduction

Cytosine arabinoside (ara-C) is effective in the treatment of leukemia and lymphoma [5, 11, 18]. The prodrug must be phosphorylated intracellularly to cytosine arabinoside triphosphate (ara-CTP), its active form. Ara-C is metabolized primarily in the liver by deamination to uracil arabinoside (ara-U), which is considered to be biologically inactive. In 1974, Momparler [12] first suggested the use of high-dose ara-C to eradicate leukemic stem cells in a short course of therapy. These high doses penetrate the blood-brain barrier, achieving significant cerebrospinal fluid (CSF) concentrations that treat CNS metastatic leukemia and lymphoma [7, 8, 16].

Primary central nervous system lymphoma (PCNSL) is a rare tumor whose incidence has markedly increased in patients presenting with acquired immunodeficiency syndrome (AIDS) and has also risen in apparently immunocompetent individuals [3, 6]. In 1985 we began a pilot protocol using chemotherapy and radiotherapy (RT) to treat all non-AIDS patients exhibiting PCNSL; this protocol included high-dose ara-C (3 g/m^2) [4]. We also studied the pharmacokinetics of ara-C and ara-U in the serum, CSF, and urine of these subjects.

Patients and methods

Patient selection. All patients presenting with histologically confirmed PCNSL who received chemotherapy and cranial RT were eligible for the pharmacokinetic study. 10 of 11 subjects consented to participate, including 7 men and 3 women whose median age was 55 years. Nine patients received ara-C as part of a regimen designed to treat PCNSL at diagnosis, and one subject received ara-C as salvage therapy for recurrent disease. At diagnosis, four patients showed cytologic evidence of leptomeningeal lymphoma, the findings of two were negative, and four exhibited suspicious or atypical lymphocytes in their CSF.

Drug administration. An Ommaya reservoir was placed in all patients on the protocol. Therapy included preradiation systemic (1 g/m^2) and intra-Ommaya methotrexate (12 mg/dose) followed by 4,000 cGy whole-brain RT along with a 1,440-cGy boost to the tumor bed [4]. After completion of cranial RT, patients received two courses of high-dose ara-C; each course consisted of two doses of 3 g/m^2 ara-C given as a 3-h i.v. infusion separated by a 24-h interval. The two courses were separated by 3–4 weeks, depending on recovery of the peripheral blood counts. Six of ten patients completed the pharmacokinetics study for both courses of ara-C (four infusions), three subjects completed the study for one course (two infusions), and samples were obtained from one individual during one ara-C infusion. Therefore, data on 31 infusions of high-dose ara-C were analyzed. Ara-U levels were measured in the same plasma samples from nine patients and in the CSF samples from two subjects.

Sample collection. Blood samples (10 ml) were collected in heparinized tubes and immediately centrifuged at 3,000 *g* for 10 min, and 2 ml plasma was put into tubes containing 0.5 mg tetrahydrouridine (THU). Samples were taken from two patients at time zero (before the infusion) and at 1, 2, 3, 3.25, 3.5, 4, 6, and 24 h; specimens were obtained from the remaining eight subjects at 0, 3, 6, and 24 h. At the same time points, CSF samples were taken from the Ommaya reservoir. Before each CSF sample was drawn, a 4-ml aliquot was taken from the reservoir and

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Table 1. Mean ara-C concentrations for all patients over a 2-day course of treatment

Sampling time	Plasma ($n = 10$)	CSF ($n = 10$)	Plasma/CSF ara-C ratio
Day 1:			
0 h	0.001 ± 0.003	0.001 ± 0.005	0.93
3 h	10.890 ± 10.79	1.578 ± 1.49	6.9
6 h	0.104 ± 0.006	0.403 ± 0.215	0.26
24 h	0.035 ± 0.088	0.008 ± 0.011	4.2
Day 2:			
3 h	10.979 ± 8.833	1.283 ± 0.479	8.6
6 h	0.273 ± 0.486	0.471 ± 0.192	0.58
24 h	0.011 ± 0.01	0.006 ± 0.004	1.9

Data represent mean values ± SD expressed in μg/ml

discarded; the following 2 ml aliquot was collected and put into heparinized tubes containing 0.5 mg THU. Urine was collected over 24 h. Plasma, CSF, and 10-ml aliquots of urine were stored at −20° C pending analysis.

Analysis of ara-C and ara-U. For the assay of ara-C, the radioimmunoassay technique of Piall et al. [13] was used. Antibody for the radioimmunoassay was purchased from the University of Surrey, Guilford, England. Separate standard curves were used for the evaluation of ara-C levels in plasma and urine. The sensitivity of the assay was 0.6 μg/ml. For the assay of ara-U, 6 μg 2′-deoxyuridine (dUR; Calbiochem, San Diego, Calif.) and 2 ml 6% cold trichloroacetic acid (TCA) were added per milliliter of each sample, which was then mixed and centrifuged for 10 min at 3,000 rpm. To the supernatant, 2 ml freshly prepared Freon amine solution [1,1,2-trichloratrifluoroethane + trioctylamine, 5 : 1 (v/v)] (Aldrich Chemical Inc., Milwaukee, Wis.) was added twice for the extraction of TCA. After centrifugation, the supernatant was filtered through a 0.45-μm Millipore filter (Nikon Millipore Kogyo, Yonezawa, Japan). The separation of ara-C, ara-U, and dUR was performed on a Beckman C_{18} ultrasphere ODS 5-μm column (Beckman, San Remo, Calif.) by elution with 0.01 M ammonium phosphate (pH 5.1) containing 1% methanol. Calculation was based on the ratios of AUC_{dUR} over $AUC_{ara\text{-}U}$ as evaluated in the UV range at 265 nm. The sensitivity of the assay for ara-U was 0.25 μg/ml.

Pharmacokinetic calculations. AUC values for ara-C and ara-U in plasma and CSF were calculated using the formula:
$AUC = AUC_{0-24\,h} + C_{24\,h}/k$,
where $AUC_{0-24\,h}$ was calculated by the linear trapezoidal rule, $C_{24\,h}$ was the concentration at 24 h, and k was the terminal rate constant determined from the slope of the terminal log-linear region of the plasma data. The renal clearance (RC) of ara-C was calculated as the amount of drug excreted in the urine divided by the corresponding AUC. The total-body clearance (TBC) of ara-C was calculated as the delivered dose divided by the AUC. The terminal half-lives of ara-C and ara-U were determined by dividing 0.693 by their terminal rate-constant k.

Results

Pharmacokinetics of ara-C

The mean plasma and CSF ara-C concentrations for all patients at the major time points are outlined in Table 1. Mean plasma ara-C levels reached 10.89, 0.1, and 0.035 μg/ml at 3, 6, and 24 h, respectively, on day 1, with comparable levels being measured on day 2 (Table 1).

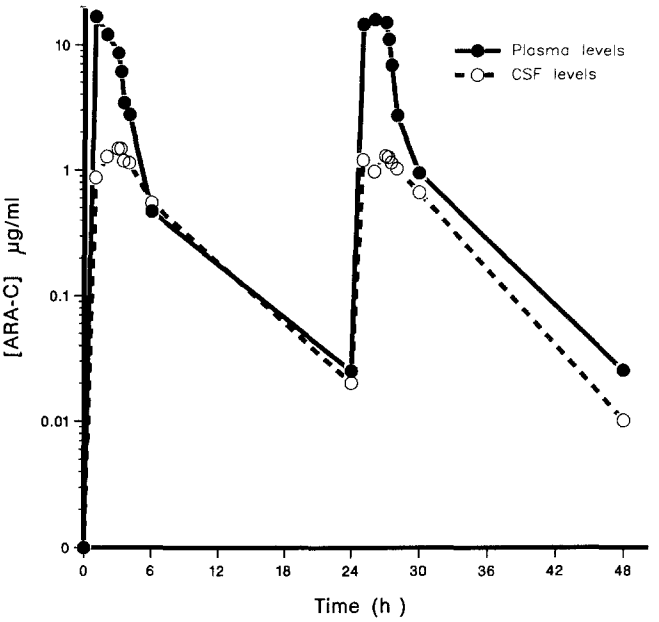

Fig. 1. Mean plasma and CSF ara-C levels in 2 patients undergoing extensive sampling

Mean peak CSF ara-C levels (3 h) amounted to 12%–14% of the simultaneous plasma levels, resulting in plasma/CSF ratios of 6.9 (day 1) and 8.6 (day 2); however, at 3 h after completion of the drug infusion (6-h time point), CSF levels were 1.7–3.9 times higher than the corresponding plasma levels, resulting in plasma/CSF ratios of 0.26 and 0.58 on days 1 and 2, respectively. By 24 h, plasma and CSF levels of ara-C had dropped substantially and the plasma/CSF ratio was 4.2–1.9.

The time course of plasma and CSF ara-C concentrations are shown for the two patients who underwent more frequent sampling (Fig. 1). The plasma ara-C level rose immediately to reach a peak of about 10 μg/ml (41 μM) within 1 h, which was maintained steadily throughout the infusion (Fig. 1). Thereafter, the ara-C concentration fell rapidly, decreasing by 75% within 1 h of completion of the infusion (4-h time point). The CSF level rose similarly within 1 h, but peak levels amounted to only about 10% of the corresponding plasma peaks. The CSF concentration was consistently maintained over 4 h but dropped to 50% of the initial value at 6 h. Thereafter, both plasma and CSF ara-C levels were rapidly cleared, and only small amounts remained at the end of the dosing interval (24 h). For this reason, data obtained on each day of ara-C administration for both courses were pooled for calculation of the area under the curve (AUC) and clearance (Table 2).

The data collected from the two patients who underwent extensive sampling are shown separately from those collected from the remaining eight subjects (Table 2). The plasma ara-C AUC values were comparable for both groups, averaging 55.4 and 30 μg h ml^{-1}, respectively. On average, 4%–6% of each dose was excreted unchanged in the urine over 24 h. The mean RC value ranged from 6.5 to 23.9 l/h, and the TBC value averaged 103–475 l/h. Although a correlation between the TBC value and the patient's body surface area and weight was observed, it

Table 2. Pharmacokinetics of ara-C in patients undergoing limited and extensive sampling

	23 infusions (8 patients)	8 infusions (2 patients)
Plasma and urinary ara-C:		
C_p3h (μg/ml)	9.54 ± 10.96	11.7 ± 5.7
AUC (μg h ml^{-1})	30 ± 32.7	55.4 ± 17.4
Amount excreted (mg)	213.7 ±130.7	294.4 ±211.1
% Excreted over 24 h	4 ± 2.4	5.4 ± 3.3
RC (l/h)	23.9 ± 32.6	6.5 ± 5.4
TBC (l/h)	475 ±552	103 ± 34
$t_{1/2}$ (h)	–	3.33
CSF ara-C:		
$C_{CSF}3h$ (μg/ml)	1.49 ± 1.24	1.38 ± 0.25
AUC (μg h ml^{-1})	8.79 ± 4.11	9.7 ± 5.6
$t_{1/2}$ (h)	–	3.57

Data represent mean values ± SD. C_p3h, Plasma concentration at 3 h (end of the infusion); AUC, area under the curve at 0–24 h; RC, renal clearance; TBC, total body clearance; $C_{CSF}3h$, CSF concentration at 3 h

Table 3. Mean ara-U concentration in 9 patients

Sampling time	Plasma ($n = 9$)	CSF ($n = 2$)	Plasma/CSF ara-U ratio
Day 1:			
0 h	0.33 ± 0.8	0 ± –	–
3 h	104.2 ±19.7	9.32±3.26	11.2
6 h	59.9 ±21.5	19.55±7.59	3.1
24 h	6.1 ± 2.8	2.74±1.6	2.2
Day 2:			
3 h	108.4 ±26.3	13.08±4.74	8.3
6 h	67.7 ±15.6	17.63±8.71	3.8
24 h	4.1 ± 1.8	2.24±2.95	1.8

Data represent mean values ±SD expressed in μg/ml

was not significant. The $t_{1/2}$ value for ara-C elimination was 3.33 h in plasma and 3.57 h in CSF. The ratio of plasma AUC to CSF AUC averaged 3.4–5.7.

Pharmacokinetics of ara-U

The corresponding ara-U levels were measured in the plasma of nine patients and in the CSF of the two subjects who underwent extensive sampling (Table 3). The mean peak (3-h) plasma ara-U concentration was 104 μg/ml, i.e., 10 times higher than the corresponding ara-C level. Plasma levels of ara-U were higher than CSF concentrations at every time point. The time course of ara-U accumulation and clearance is shown in Fig. 2. Plasma levels of ara-U rose throughout the infusion and reached a peak at 3.25 h. In CSF, the ara-U concentrations rose steadily and reached a peak at 6 h; throughout the infusion, CSF ara-U levels were 10 times greater than the corresponding ara-C levels, and at 6 h (3 h postinfusion) they were >28 times higher. Plasma and CSF ara-U levels were rapidly cleared at the end of the dosing interval, and little accumulation was evident. The mean plasma AUC value for ara-U was 977.3–1036.8 μg h ml^{-1}, and the mean CSF AUC value

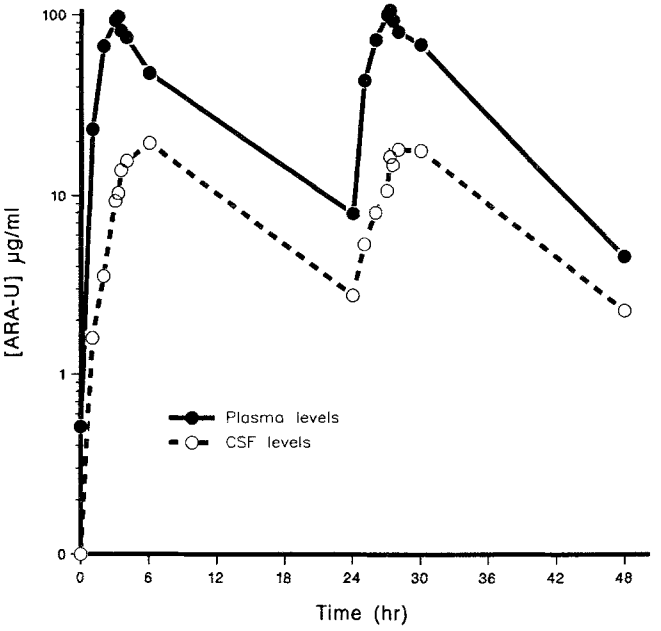

Fig. 2. Mean plasma and CSF ara-U levels in 2 patients undergoing extensive sampling

Table 4. Pharmacokinetics of ara-U in patients undergoing limited and extensive sampling

	32 infusions (7 patients)	8 infusions (2 patients)
Plasma and urinary ara-U:		
C_p3h (μg/ml)	111.5 ± 25.9	95.6 ± 8.7
AUC (μg h ml^{-1})	977.3 ± 222.6	1,036.8 ± 231.1
Amount excreted (mg)	3,750 ±2,144.1	3,940.99 ±3,633.9
% Excreted over 24 h	63.4 ± 35.1	72.56 ± 59.81
$t_{1/2}$ (h)	–	5.98
CSF ara-U:		
$C_{CSF}3h$ (μg/ml)	–	11.2 ± 4.3
AUC (μg h ml^{-1})	–	282.98 ± 110.3
$t_{1/2}$ (h)	–	6.96

Data represent mean values ± SD. C_p3h, Plasma concentration at 3 h (end of the infusion); AUC, area under the curve at 0–24 h; $C_{CSF}3h$, CSF concentration at 3 h

was 282.98 μg h ml^{-1} (Table 4). On average, 63%–73% of the ara-U was excreted within a 24-h period. The $t_{1/2}$ value for ara-U elimination was 5.98 h in plasma and 6.96 h in CSF.

Clinical response

No appreciable difference in the CSF ara-C level was observed among patients showing positive, negative, or suspicious CSF cytologic findings, although the number of subjects in each group was small. No clear correlation could be established between ara-C and ara-U levels and the response of parenchymal brain lymphoma since only three patients displayed lesions on computerized tomography (CT) scans at the time of ara-C administration. In two

Table 5. Pharmacokinetics of ara-C and ara-U in plasma and CSF

Authors	Patients (*n*)	Source of CSF	Dose of ara-C	Peak plasma ara-C (μg/ml)	AUC_{pl} (μg ml^{-1} h^{-1})	Plasma half-life (h)	Peak CSF ara-C (μg/ml)	CSF half-life (h)	Peak plasma ara-U (μg/ml)	Peak CSF ara-U (μg/ml)
Slevin et al. [20]	5	LP	3 g/m² ×3 h	9.6	35.9	2.6[a]	1.07	>2	–	–
Takashima and Matsuyana [21]	8	LP	3 g/m² ×4 h	17.38	–	–	2.13	–	–	–
Capizzi et al. [2]	2	LP	3 g/m² ×3 h	27.83 (115 μM)		1.81[a]	>0.75 (>3 μM)	–	75.7 (310 μM)	33.6–41.8 (138–171 μM)
Early et al. [5]	1	Ommaya	2 g/m² ×1 h	17.96	–	–	1.55	–	–	–
Breithaupt et al. [1]	2	LP	3 g/m² ×2–3 h	12.2–24.3 (49–97 μM)	– –	– –	1.2–3.7 (4.9–14.7 μM)	– –	94.5–110 (378–441 μM)	25 (100 μM)
Present series (31 infusions)	10	Ommaya	3 g/m² ×3 h	11.7	36.16	3.33	1.28	3.57	104.2	11.2

[a] Terminal half-life
LP, Lumbar puncture

cases, a clear CT scan was obtained at 6.5 and 15 months after the completion of both courses of ara-C, respectively, but the significance of this delayed improvement is not clear and cannot be directly attributed to ara-C administration. One patient showed no response to ara-C and died of progressive disease. Ara-C and ara-U concentrations in these three subjects were comparable with those measured in the other seven patients.

Toxicity

No patient experienced CNS toxicity following the administration of high-dose ara-C. There was one episode of mild conjunctivitis, which responded to topical corticosteroid treatment. All subjects developed myelosuppression; one patient had a culture-negative nadir fever requiring hospitalization and one required a transfusion. No other ara-C-related toxicity was noted.

Discussion

This is the first comprehensive study of concurrent plasma and CSF levels of ara-C and ara-U after high-dose ara-C administration. Prior studies of CSF ara-C concentrations focused on individual subjects or small groups displaying a heterogeneous assortment of tumors. CSF ara-C levels were often measured at only 1–2 time points during the course of ara-C infusion, in part because CSF was predominantly obtained by lumbar puncture, which made frequent sampling difficult. We sequentially studied a uniform group of patients is whom serial plasma and CSF measurements were made over repeated doses of high-dose ara-C.

High-dose ara-C (3 g/m² given as a 3-h infusion) produces high plasma and CSF levels that are maintained throughout the infusion [2, 20, 21]. Although plasma ara-C levels fall rapidly after the completion of drug administration, CSF concentrations remain elevated for 3 h after the end of the infusion. The peak plasma and CSF ara-C levels measured in the present study (11.7 and 1.28 μg/ml, respectively) compare favorably with those reported by other investigators (Table 5). At ara-C concentrations of >1 μg/ml and in the presence of optimal kinase activity, intracellular ara-CTP levels are sufficient to exert cytotoxic effects [9, 15]. The prolonged exposure to ara-C in CSF should enable the substantial intracellular accumulation of ara-CTP in the CNS.

After 3-h infusions of 3 g/m² ara-C, Capizzi et al. [2] reported average peak plasma ara-C and ara-U levels of 115 μM (27.83 μg/ml) and 310 μM (75.7 μg/ml), respectively. These values were higher than those obtained in the present study (10.8 and 109.8 μg/ml, respectively), but the peak CSF ara-C level, ≥3 μM (≥0.73 μg/ml), was comparable with our finding. The CSF ara-U levels measured by these authors in two patients at 2 and 3 h postinfusion were 137.6 and 171.4 μM (33.6 and 41.8 μg/ml); these values were higher than those obtained in the present study (13.08, 17.63, and 2.24 μg/ml at 3, 6, and 24 h, respectively), reflecting the higher plasma levels of ara-C and ara-U measured by the aforementioned investigators. The CNS exhibits little, if any, deaminase activity; therefore, ara-C entering the CNS is not metabolized to ara-U to any significant extent, although the occurrence of cytidine deaminase in the choroid plexus or at the ependymal surface cannot be excluded [10, 17]. The ara-U appearing in the CSF is probably formed systemically and enters the nervous system concomitantly with ara-C.

Ara-C must be phosphorylated to ara-CTP before it can exert its biologic effect. Recent data demonstrate that ara-CTP accumulation in human leukemic cells is saturated at plasma ara-C levels of about 5 μM (1.2 μg/ml) [14, 15]. However, ara-C concentrations that do not lead to optimal intracellular ara-CTP production can nonetheless disrupt cell function. Early studies of mouse leukemia cells revealed that ara-C concentrations of ≥1 μg/ml resulted in the death of >90% of the cells; at levels of 0.1 μg/ml, no cells were killed but a substantial reduction in DNA syn-

thesis was observed [10]. Comparable results were reported for human leukemia cells in culture. Subsequent work examined the relationship of ara-C concentration and intracellular ara-CTP production in human marrow myeloblasts. DNA synthesis was inhibited by 50% at ara-C concentrations ranging from 30 to 100 nM (0.0073–0.023 μg/ml) and by at least 85% at a concentration of 3 μM (0.73 μg/ml) [9]. Whereas plasma ara-C levels in our patients remained well above 10 μM throughout the infusion and were above 3 μM for several hours afterward, CSF levels reached a peak of 1 μg/ml (4.1 μM) during the infusion only and decreased more slowly, substantiating the need for high-dose ara-C in the treatment of CNS tumors. Our CSF measurements were performed using ventricular fluid, which rapidly leaves the ventricles and circulates in the subarachnoid space. Although ara-C concentrations were not determined in the lumbar subarachnoid space, cytotoxic ara-C levels may remain elevated in this area for a longer period since circulation is slower than CSF outflow from the ventricles. This has been established for the CSF flow of intrathecal methotrexate [19].

Few of our patients exhibited residual abnormalities on their cranial CT scan at the time of ara-C administration; consequently, correlation of the CSF ara-C level and the clinical response could not be done. The CSF ara-C levels in our patients were similar in the presence and the absence of leptomeningeal lymphoma at diagnosis. However, at the time of ara-C administration, all patients had completed cranial RT and a course of chemotherapy to treat the meninges. None showed clinical evidence of meningeal lymphoma at the beginning of the ara-C infusion. Therefore, it is likely that our data represent the penetration of an intact blood-brain barrier by high-dose ara-C. The CSF levels found in the present study are comparable with those previously measured in patients presenting with known meningeal leukemia and lymphoma, suggesting that active tumor is not necessary to ensure adequate CSF penetration by high-dose ara-C [5, 16].

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