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Clinical pharmacology of N^4-palmitoyl-1-β-D-arabinofuranosylcytosine in patients with hematologic malignancies

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Summary. The pharmacokinetics of oral N^4-palmitoyl-1-β-D-arabinofuranosylcytosine (PLAC), a lipophilic and deaminase-resistant derivative of 1-β-D-arabinofuranosylcytosine (ara-C), were determined in patients with hematologic malignancies. The concentration of ara-C and 1-β-D-arabinofuranosyluracil (ara-U), metabolites of PLAC, were measured by radioimmunoassay and gas chromatography-mass spectrometry-mass fragmentography, respectively. The concentration of PLAC was determined by measuring ara-C, which was derived from PLAC by hydrolyzation. In six patients given an oral bolus of PLAC (300 mg/m^2), the plasma-disappearance curve of PLAC corresponded to a one-compartment open model, including first-order absorption. The peak plasma level was 22.9 ± 6.4 ng/ml, and the predicted time to reach the peak level was 2.5 ± 1.0 h. The elimination half-life was 3.8 ± 2.7 h. The plasma ara-C level increased slowly to 6.9 ng/ml during the 1st 2–3 h after administration and remained over 1.0 ng/ml for 12 h. Plasma ara-U was detectable for at least 24 h, with a peak concentration of 376 ng/ml at 6 h. Urinary PLAC excretion was below the limit of detection (5 ng/ml) in all cases. Prolonged urinary ara-C and ara-U excretion was detected, but the total recovery rate was low (6.7% in 24 h) and varied between patients. In spite of the lipophilic nature of the drug, the PLAC concentration in the cerebrospinal fluid, measured at 3 or 6 h, was below the limit of detection in all four patients with no meningeal involvement. This study showed low but persistent levels of PLAC in plasma and tissues, with a continuous release of small amounts of ara-C, which demonstrated antitumor activity in patients with hematologic malignancies.

Introduction

1-β-D-Arabinofuranosylcytosine (ara-C) is one of the most useful drugs for the treatment of patients with acute leukemia or lymphoma [5]. However, in humans this drug has a short half-life as a result of its conversion by cytidine deaminase to 1-β-D-arabinofuranosyluracil (ara-U), an inactive metabolite of ara-C [4, 9, 17]. Several attempts have been made to overcome this limitation [3, 11, 16]. N^4-acyl-ara-C is a derivative of ara-C with a long-chain fatty acid introduced at the N^4-position. It is deaminase-resistant and also has high lipophilicity and a long half-life compared with ara-C [1, 2]. Among the N^4-acyl-ara-C derivatives, N^4-behenoyl-1-β-D-arabinofuranosylcytosine (BHAC) has been used clinically by intravenous infusion and has shown a therapeutic effect equivalent to that of ara-C [15], with fewer side effects. We have reported the results of a precise pharmacological study of BHAC [18, 24].

N^4-palmitoyl-1-β-D-arabinofuranosylcytosine (PLAC) is another acyl-ara-C derivative. Besides the unique therapeutic advantages of N^4-acyl-ara-C derivatives vs ara-C, this drug offers patients another benefit: it is given orally. According to a preclinical study [10], PLAC is absorbed from the gastrointestinal tract and small amounts of ara-C are released slowly. Phase I and II clinical studies carried out in Japan have shown promising results with tolerable side effects in patients with hematologic malignancies, including acute leukemia, myelodysplastic syndrome, and myeloproliferative disorder [14, 19]. A comprehensive pharmacokinetic study of oral PLAC was carried out in patients with hematologic malignancies to determine an appropriate schedule for administration.

Materials and methods

PLAC was kindly supplied by Asahi Chemical Industry Co., Ltd. (Tokyo, Japan), as 50-, 100-, and 200-mg capsules containing dioctyl sodium sulfosuccinate (Nikkol OTP-100S; Nihon Surfactant Kogyo K. K., Tokyo, Japan) and polyoxyethylene 40 stearate (Nikkol MYS-40; Nihon Surfactant Kogyo K. K., Tokyo, Japan) as a detergent and stabilizer.

Patients. All patients eligible for this study were diagnosed as having hematologic malignancies by the usual hematologic and clinical criteria (Table 1). Informed consent for this investigation was obtained from each patient or his family prior to drug treatment and pharmacokinetic evaluation. None of the patients had hepatic or renal dysfunction, as determined by a serum bilirubin value of ≥ 2.0 mg/dl and a serum creatinine level of ≥ 1.5 mg/dl. No other drugs were given until sample collection was completed.

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Table 1. Patient characteristics

Patient	Type of malignancy	Age (years)	Sex	Weight (kg)	WBC counts (cells/μl)	Hb (g/dl)	Bilirubin (mg/dl)	Serum creatinine (mg/dl)
1	ANLL	39	M	62.0	3,100	14.2	0.4	1.1
2	ALL	35	F	57.0	1,000	12.1	0.8	0.7
3	CML	45	F	47.0	44,200	7.0	0.3	1.3
4	Hypoplastic leukemia	72	M	39.5	1,400	7.7	0.3	0.7
5	Polycythemia vera	64	F	56.0	19,300	13.8	0.2	0.8
6	Polycythemia vera	64	F	50.0	17,800	15.0	0.4	0.8

ANLL, acute nonlymphocytic leukemia; ALL, acute lymphatic leukemia; CML, chronic myelogenous leukemia; Hb, hemoglobin

PLAC administration and sample collection. PLAC was given orally as a bolus with 200 ml H_2O after an overnight fast. Patients were allowed to resume normal p.o. intake 2 h after drug administration. Blood samples were collected at designated intervals for 24 h in heparinized tubes containing tetrahydrouridine, an inhibitor of cytidine deaminase, at a final concentration of 0.1 m*M* [9]; they were immediately put on ice. Plasma samples were then separated by centrifugation at 4° C (700 *g*, 10 min). Urine samples were also collected at designated intervals for 24 h. Samples of plasma and urine were stored at −20° C until the assays for PLAC, ara-C, and ara-U were carried out. For the assay of drug concentration in the cerebrospinal fluid (CSF), spinal taps were carried out in four patients who had acute leukemia with no meningeal involvement at 3 or 6 h after PLAC administration; 2 ml liquid was collected in tubes containing tetrahydrouridine (0.1 m*M*).

Determination of concentrations of PLAC, ara-C, and ara-U. PLAC concentration in the samples was determined by a method described in detail elsewhere [19]. Briefly, PLAC was hydrolyzed by sodium hydroxide to ara-C, and the latter was measured by radioimmunoassay. A 1-ml plasma samples was diluted with an equal volume of 0.9% sodium chloride and 10 μl ethanol and was mixed with 2 ml methanol and 4 ml chloroform. After sonication and centrifugation, the chloroform layer was collected and 3 ml was mixed with 2 ml methanol and 0.2 ml 0.2 *N* sodium hydroxide, kept overnight at 37° C, and dried in vacuo. Thus, PLAC was hydrolyzed and recovered as ara-C. The residue was mixed with 1 ml 0.01 *M* phosphate-buffered saline (pH 7.4) containing 0.5% bovine serum albumin, then sonicated and centrifuged. The ara-C concentration in the supernatant was determined by the radioimmunoassay method of Shimada et al. [20]; the limit of detection was 1 ng/ml for ara-C and 5 ng/ml for PLAC.

The ara-C concentration in the samples was determined directly by the radioimmunoassay method described above; the limit of detection was 1 ng/ml. The ara-U concentration in the samples was determined by the method of Mizuno et al., using a gas chromatography-mass spectrometry-mass fragmentography procedure described elsewhere [24]; the limit of detection was 10 ng/ml.

Analysis of the plasma PLAC concentration. Plasma concentrations (Ct) of PLAC after a single oral dose were fitted to a one-compartment open model, including first-order absorption, as described by the following equation [6]:

$$Ct = \frac{F \cdot D \cdot Ka}{Vd\,(Ka - Kel)} [e^{-K_{el}(t-t_o)} - e^{-K_a(t-t_o)}],$$

where K_a is the apparent first-order absorption rate constant, K_{el} is the apparent first-order elimination rate constant, V_d is the apparent volume of distribution, F is the apparent fraction of the available dose (which could not be determined in this case), D is the dose given, and t_o is the lag time preceding the initiation of absorption.

The predicted time of the peak plasma level (C_{max}) after administration (T_{max}) was calculated as the time when $dCt/dt = 0$. The elimination half-life was calculated as $0.693/K_{el}$. The AUC from time zero to infinity (AUC_{inf}) was computed using the trapezoidal rule. The total plasma clearance (Cl_{tot}/F) was estimated from D/AUC_{inf}. The plasma PLAC concentration data was analyzed by nonlinear least-squares regression analysis, MULTI [28], including Akaike's information criterion [27].

Results

Plasma PLAC levels

The pharmacokinetic parameters obtained by computer analysis of the plasma PLAC concentration-vs-time curve (Fig. 1) are summarized in Table 2.

The curves corresponded to a one-compartment open model with first-order absorption. C_{max} of PLAC varied from 16.2 to 33.7 μg/l, with a mean ± SD of 22.9 ± 6.4 μg/l. T_{max} was 2.5 ± 1.0 h. The plasma $t_{1/2}$ for PLAC varied from patient to patient (range, 1.4–6.6 h), with an average of 3.8 ± 2.7 h. The mean ±SD of V_d/F was 262 ± 148 l/kg (range, 178–556 l/kg), and the mean AUC was 174 μg·h/l. The total clearance (Cl_{tot}/F) was 63.4 ± 33.6 l/h per kg.

Urinary excretion of PLAC, ara-C, and ara-U

Unchanged PLAC was not excreted in the urine in any patient. However, in 24 h, 0.05% of the dose appeared as ara-C and 6.67%, as ara-U; thus, 6.72% of PLAC was eliminated in the urine in 24 h.

Plasma levels of ara-C and ara-U

The plasma concentration of ara-C, the active metabolite of PLAC, was measured in the same samples as were used for calculating plasma PLAC levels (Fig. 1). The concentration of ara-C increased slowly to 6.9 ± 4.8 ng/ml during the 1st 2–3 h after administration and was maintained for 12 h after drug administration. The apparent mean half-life for ara-C, calculated in four cases (patients 2, 4, 5, and 6), was 2.49 h. Plasma ara-U was detectable for at least

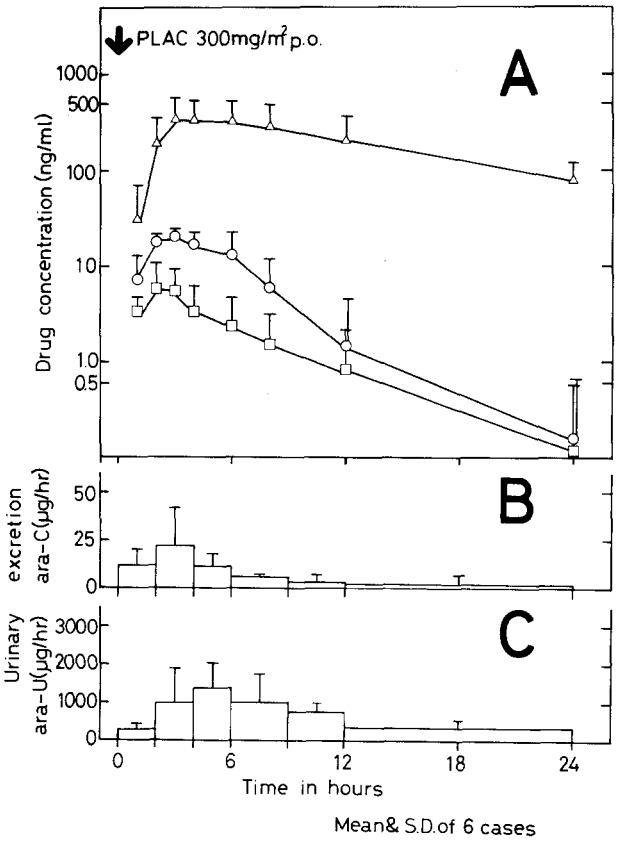

Fig. 1. A Plasma PLAC, ara-C, and ara-U concentrations in six patients following a p.o. bolus of PLAC (300 mg/m^2). ○, plasma PLAC concentration; □, plasma ara-C concentration; △, plasma ara-U concentration (mean of six patients). *Bars* = 1 SD. **B, C** Urinary ara-C and ara-U excretion, respectively, in six patients. *Columns* represent the mean of six patients; *bars* = 1 SD

24 h after administration. Its peak concentration was 376 ± 150 ng/ml at 6 h, which was 3–4 h later than the T_{max} for ara-C (Fig. 1).

CSF levels of PLAC, ara-C, and ara-U

The CSF concentrations of PLAC and its metabolites were measured 3 or 6 h after administration in four patients who had no meningeal involvement (Table 3). PLAC was not detected in any of these four patients (< 5 ng/ml), nor was ara-C detected in three of four patients, in spite of a lower limit of detection (0.15 ng/ml) in the CSF vs plasma. However, ara-U was detected in three of four patients at concentrations of 133–523 ng/ml.

Discussion

The present studies demonstrated that in patients with hematologic malignancies, oral PLAC was absorbed from the gastrointestinal tract, slowly releasing ara-C, an active metabolite. Ara-C was subsequently converted to ara-U, an inactive metabolite.

Interpatient differences in AUC and C_{max} were in the 4-fold and 2-fold range, respectively (Table 2); this suggests that the interpatient bioavailability of PLAC was quite variable, although we cannot know the exact bioavailability because i.v. infusion has not yet been tried in humans. As neither the AUC nor the C_{max} showed either a positive or negative correlation with the formation and excretion of ara-C and ara-U (Table 2), this variability was thought to be due to a number of different and independent factors, such as the absorption rate and drug metabolism.

The total recovery of urinary PLAC, including unchanged drug, ara-C, and ara-U, was only 6.72%, suggesting poor absorption from the gastrointestinal tract. Of

Table 2. Pharmacokinetic parameters of PLAC in each patient

Patient	Dose:			K_a (h^{-1})	$t_{1/2}$ (h)	V_d/F (l/kg)	T_{max} (h)	C_{max} (μg/l)	AUC_{inf} (μg·h/l)	Cl_{tot}/F (l/h per kg)	Lag time (h)
	(mg)	(mg/kg)	(mg/m^2)								
1	450	7.3	300	0.43	4.17	178	2.55	22.4	245.3	29.6	−1.06
2	450	7.9	300	0.75	1.72	239	2.53	16.2	82.0	96.3	0.74
3	400	8.5	300	8.92	1.43	214	2.28	33.7	82.5	103.1	1.94
4	400	10.1	300	5.06	7.53	556	1.26	16.9	198.1	51.1	0.46
5	450	8.0	300	0.85	1.40	154	2.40	24.6	105.6	76.1	0.88
6	400	8.0	300	0.61	6.60	233	4.22	23.9	327.8	24.4	0.74
Mean ± SD				2.77 ±3.49	3.81 ±2.74	262 ±148	2.54 ±0.95	22.9 ±6.4	173.6 ±100.8	63.4 ±33.6	0.62 ±0.97

Table 3. CSF concentrations of PLAC and its metabolites

Patient	Age (years)	Sex	Dose (mg/m^2)	Time after administration (h)	PLAC level (μg/ml)		ara-C level (μg/ml)		ara-U level (μg/ml)	
					CSF	Plasma	CSF	Plasma	CSF	Plasma
RI	47	M	300	3	ND[a]	8.24	ND	9.72	133	267
TM	37	F	300	6	ND	28.3	2.37	5.50	523	676
HU	57	F	300	6	ND	60.4	ND	3.86	170	514
KU	38	M	300	6	ND	12.0	ND	1.24	ND	199

[a] ND, not detected. Limits of detection of PLAC, ara-C, and ara-U in CSF were 5, 0.14, and 10 ng/ml, respectively

course, 24-h urinary excretion did not fully reflect gastrointestinal absorption; for example, some of the absorbed drug might have been excreted in the feces with bile. The plasma ara-U concentration at 24 h was still 85.2 ± 37.4 ng/ml, suggesting the continued release of metabolites from PLAC, which remained in the liver and other tissues even after 24 h.

The PLAC/ara-U ratio at the measured PLAC T_{max} was 0.06 and was usually < 0.2, indicating the relatively rapid metabolism of PLAC. This was mainly due to first-pass metabolism of PLAC in the liver, with high levels of deacylation [21] and deamination [8]; the small intestine might also have played some role [10]. PLAC has been reported to metabolize directly to form ara-C and palmitic acid in mouse liver [21]. The apparent $t_{1/2}$ for ara-C derived from PLAC was 2.49 h, which was longer than that for nonderivative ara-C (111 min) [9].

The V_d/F was very high (262.1 ± 147.5 l/kg) for this drug. A low absorption rate and high rate of first-pass metabolism in the liver, discussed above, might explain this result. The conversion of PLAC to ara-C and then to ara-U during absorption from the gastrointestinal tract, as reported in mice [10], could be another reason. Unchanged drug was not excreted in the urine in any significant amount, as was the case with BHAC [24]. Possibly, PLAC could not be filtered by the renal glomerulus because it might be bound tightly to plasma proteins and blood cells, as is BHAC [24, 25], or perhaps almost all of the filtered PLAC was reabsorbed from the renal tubules due to its lipophilicity [26].

In spite of the lipophilic nature of this agent, hardly any PLAC penetrated the blood-brain barrier. The ara-U detected in the CSF was believed to have been derived from plasma ara-U, because both PLAC and ara-C were almost undetectable in the CSF and cytidine deaminase activity was very low [8]. This low rate of CSF ara-C detection suggests that CNS prophylaxis by this drug would be ineffective.

In the previous phase II study of PLAC [14], complete remission was achieved in 14% of 76 patients with acute nonlymphocytic leukemia, and 4 of 50 patients with myelodysplastic syndrome showed a good response to the oral ara-C analog. PLAC has two possible mechanisms of action. The first possibility is induction of cellular differentiation. The effect of PLAC was comparable with that of low-dose ara-C therapy [12] because of similar, persistent, low concentrations of ara-C in both therapies. Low-dose ara-C therapy may induce differentiation in malignant cells. However, Ishikura et al. [13] reported that the conventional dose of ara-C in this therapy (10 mg/m^2 s.c.) can yield a maximal serum concentration of 52–132 ng/ml, which would effectively inhibit DNA synthesis, suggesting an antimitotic mechanism of action [7]. In the case of PLAC therapy, the peak concentration of released ara-C was quite low: 1.8–14.7 ng/ml (mean ± SD, 6.9 ± 4.8 ng/ml). Thus, from the viewpoint of inducing cellular differentiation, PLAC might be an effective approach. We have reported a case of hypoplastic leukemia in which complete remission was achieved by PLAC therapy (150 mg/day p.o.) without severe bone marrow aplasia [23].

However, another mechanism of action should also be considered. The phase II study of PLAC showed an adequate cytoreduction effect in some patients. Leukopenia and thrombocytopenia have also been reported as side effects [14], suggesting a possible antimitotic effect of PLAC. Judging from the report of Harris and Grahame-Smith [7], plasma concentrations of ara-C derived from PLAC were too low to show substantial cytostatic effect, which suggests intracellular activation of PLAC in tumor cells. Tsuruo et al. [22] have reported that PLAC possessed an affinity for the KB-cell plasma membrane and was slowly deacylated to ara-C in these cells. This affinity and intracellular conversion to ara-C might contribute to the cytotoxic effect of PLAC. Further pharmacologic studies should be done to clarify the exact mechanism of action of PLAC in vivo.

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