

# Pharmacokinetic Study of Oral and Bolus Intravenous 2-Chlorodeoxyadenosine in Patients With Malignancy

By Alan Saven, Wing K. Cheung, Ian Smith, Michael Moyer, Tricia Johannsen, Esther Rose, Russell Gollard, Michael Kosty, William E. Miller, and Lawrence D. Piro

**Purpose:** This study was designed to evaluate the absolute bioavailability (F value) of 2-chlorodeoxyadenosine (cladribine; 2-CdA) after multiple oral administrations, and the intersubject variability after oral and 2-hour intravenous (IV) administration schedules in patients with malignancy.

**Patients and Methods:** Patients with advanced malignancies were eligible. There were two treatment cycles; during cycle 1, patients received 2-CdA solution at 0.28 mg/kg/d orally under fasting conditions for 5 consecutive days concomitantly with omeprazole, and 4 weeks later during cycle 2 patients received 2-CdA as a 2-hour IV infusion of 0.14 mg/kg/d for 5 consecutive days. Serial blood samples for 2-CdA plasma levels were obtained after drug administrations on days 1 and 5 during each treatment cycle.

**Results:** Ten patients completed cycles 1 and 2. The F value of oral 2-CdA measured on days 1 and 5 was 37.2% and 36.7%, respectively. For both oral and IV multiple administrations, there was no significant accumulation

in maximum concentration ( $C_{max}$ ), and the intersubject variabilities (coefficient of variation [CV], ~ 40%) in  $C_{max}$  and area under the concentration-time curve from 0 to 24 hours [ $AUC_{[0-24]}$ ] values were comparable for both routes on days 1 and 5. A three-compartment open model was applied to the plasma concentration data after oral and IV administrations and resulted in good agreement between observed and simulated concentration-time profiles. Neutropenia was the principal adverse event observed when 2-CdA was administered orally and IV.

**Conclusion:** The F value of 2-CdA after oral administration was approximately 37% and there were no cumulative differences in bioavailability observed on multiple dosing of the drug. The absorption and disposition characteristics of oral 2-CdA were linear and predictable with this dosing regimen.

*J Clin Oncol 14:978-983. © 1996 by American Society of Clinical Oncology.*

**2-CHLORODEOXYADENOSINE** (cladribine; 2-CdA) is a purine analog resistant to the action of adenosine deaminase. It is cytotoxic to both resting and proliferating lymphocytes,<sup>1,2</sup> which may be especially important in the treatment of indolent lymphoproliferative disorders such as hairy cell leukemia,<sup>3-6</sup> chronic lymphocytic leukemia,<sup>7-10</sup> and low-grade non-Hodgkin's lymphoma.<sup>11-14</sup> 2-CdA has been approved in the United States for the treatment of hairy cell leukemia as a single 7-day continuous intravenous (IV) infusion at a dose of 0.09 mg/kg/d. Liliemark et al<sup>15</sup> estimated that the oral bioavailability (F value) of a phosphate-buffered solution of 2-CdA was 48% when given at a dose of 0.14 mg/kg/d for 5 days, and 55% at a dose of 0.28 mg/kg/d. The F value of 2-CdA after subcutaneous administration was approximately 100%.<sup>15</sup> In that study, the variability in area under the plasma concentration-time curve (AUC) was similar after IV, subcutaneous, and oral administrations.

We performed this study to determine the absolute bioavailability of 2-CdA after multiple oral administrations in patients with malignancy, and to determine the intersubject pharmacokinetic variability after 2-hour IV infusions and oral dosings.

## PATIENTS AND METHODS

### Patient Selection

Patients with advanced and assessable malignancies (hematologic and nonhematologic) that had failed to respond to standard therapy were eligible. Inclusion criteria included a life expectancy  $\geq$  3 months, absence of active infection, adequate renal (serum creatinine concentration  $<$  2.0 mg/dL) and hepatic functions (bilirubin, alkaline phosphatase, AST, and ALT  $<$  two times normal), adequate baseline hematologic parameters (absolute neutrophil count  $>$   $1.5 \times 10^9/L$ , hemoglobin concentration  $>$  9 g/dL, and platelet count  $>$   $60 \times 10^9/L$ ), and a Karnofsky performance status  $\geq$  60. Patients were removed from other systemic therapies for at least 4 weeks before study entry. This study was approved by the Human Subjects Committee of Scripps Clinic and Research Foundation and all patients gave written informed consent.

### Study Design

There were two treatment cycles of 2-CdA; during cycle 1 patients received oral administrations at 0.28 mg/kg/d for 5 consecutive days, and during cycle 2 patients received 2-hour IV infusions at 0.14 mg/kg/d for 5 consecutive days, 4 weeks later. The planned accrual was for 10 patients to complete both cycles 1 and 2. 2-CdA was supplied as a 1.0-mg/mL solution (Leustatin; Ortho Biotech, Raritan, NJ). During the oral dosing phase, after an overnight fast, patients swished for 20 seconds and then swallowed the appropriate amount of 2-CdA solution before being washed down with 50 to 100 mL

From the Division of Hematology and Oncology, Ida M. and Cecil H. Green Cancer Center, Scripps Clinic and Research Foundation, La Jolla, CA; and R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ.

Submitted July 5, 1995; accepted October 3, 1995.

Address reprint requests to Alan Saven, MD, Division of Hematology and Oncology, MS312, Ida M. and Cecil H. Green Cancer Center, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla, CA 92037.

© 1996 by American Society of Clinical Oncology.

0732-183X/96/1403-0038\$3.00/0

of water. Since it is believed that 2-CdA is unstable in an acid environment, patients were placed on omeprazole (Prilosec, Merck Sharp and Dohme, West Point, PA) 20 mg/d for 5 days 2 hours before receiving of oral 2-CdA. The IV solution was prepared by dissolving the calculated dose of 2-CdA in 250 mL of 0.9% sodium chloride solution.

### Pretreatment and Follow-Up Studies

History, physical examination, routine laboratory studies, and a chest x-ray were performed at baseline. Routine laboratory studies included a complete blood cell count (CBC) with a WBC differential, a chemistry-24 panel (includes electrolytes, urea, creatinine, glucose, total protein, albumin, calcium, phosphate, uric acid, alkaline phosphatase, total bilirubin, AST, and ALT), and urinalysis. In the absence of clinically assessable disease, a computed tomographic (CT) scan of sites of disease involvement was performed. The history and physical examination were repeated before each cycle of 2-CdA and monthly thereafter; the CBC count with WBC differential was performed daily during therapy and weekly thereafter; the chemistry-24 panel was redrawn on the first and fifth day of drug administration and monthly thereafter; and the urinalysis was repeated on the first day of each 2-CdA cycle. Chest x-ray and CT scans were repeated, when appropriate, to determine response status.

Hematologic and nonhematologic toxicities were evaluated according to Eastern Cooperative Oncology Group (ECOG) toxicity criteria.<sup>16</sup> Grade 3 and 4 toxicities were deemed significant. Responses were determined according to the standard response criteria used for evaluation of that particular malignancy. Patients with evidence of response 4 weeks after the second cycle, and on every second cycle thereafter, could continue to receive 2-hour infusions of 2-CdA off protocol for a maximum of six cycles.

### Pharmacologic Studies

Serial blood samples for 2-CdA plasma concentrations were obtained on days 1 and 5 during each treatment cycle. Five-milliliter samples of blood were collected and placed into edathamil (EDTA)-containing tubes predose, at 15 and 30 minutes after dosing, and at 1, 1.5, 2, 4, 6, 9, 12, 18, and 24 hours postdose. Tubes were immediately put into ice water or refrigerated and the plasma collected by centrifugation (5 minutes, 1,000g at 4°C) and then frozen at -20°C until analysis.

Plasma samples were analyzed for 2-CdA by a sensitive and specific, validated high-performance liquid chromatography mass spectrometry (LCMS) assay.<sup>17,18</sup> The samples were extracted before analysis, and the range of the standard curve was 0.05 to 20 ng/mL with a 0.05 ng/mL limit of quantitation. The interday precision (percent coefficient of variation [CV]) of the assay was less than 3% across the range of the standard curve. The accuracy of the assay was similarly within 3.5% of target concentrations. Quality-control samples were run throughout the analysis of unknown samples. The stability of 2-CdA in frozen plasma samples was confirmed, together with the stability during three freeze-thaw cycles of the samples.

### Pharmacokinetic Analysis

*Noncompartmental data analysis.* The following model-independent pharmacokinetic parameters were determined:  $C_{max}$ ,  $T_{max}$ ,  $AUC_{(0-24)}$ , and  $F$ , where  $C_{max}$  was the observed peak plasma concentration,  $T_{max}$  was the time at which  $C_{max}$  occurred,  $AUC_{(0-24)}$  was the area under the concentration-time curve during a dosing interval (24 hours), and  $F$  was the bioavailability.  $AUC_{(0-24)}$  was calculated using

PCNONLIN, version 4.2 (SCI Software, Lexington, KY).  $F$  values for days 1 and 5 were calculated as dose-normalized oral-to-IV ratios of  $AUC_{(0-24)}$  on days 1 and 5, respectively. CVs for these pharmacokinetic parameters were calculated to determine interindividual variability.

*Compartmental data analysis.* For the IV route a three-compartment open model was applied to the day 5 IV concentrations using PCNONLIN, version 4.2 (model 19). Time elapsed after initiation of the first IV infusion was used in the model fitting. The following macro constants and pharmacokinetic parameters were determined: intercompartmental macro constants ( $K_{10}$ ,  $K_{12}$ ,  $K_{21}$ ,  $K_{13}$ , and  $K_{31}$ ); half-life for each of the  $\alpha$ ,  $\beta$ , and  $\gamma$  phases of the concentration-time curve ( $T_{1/2\alpha}$ ,  $T_{1/2\beta}$ , and  $T_{1/2\gamma}$ , respectively);  $AUC$  from time-zero to time-infinity ( $AUC_{0-\infty}$ ); plasma clearance (CL); apparent volume of distribution in the central compartment ( $V_c$ ); and apparent volume of distribution at steady-state ( $V_{ss}$ ).

The day 5 plasma 2-CdA concentrations after IV infusion were used to predict the concentration-time profiles after 2-hour intravenous infusions of 0.14 mg/kg/d for 5 consecutive days. Macro constants from individual patients were used in the simulations.

For the oral route absorption rate constants ( $K_a$ ) for the oral absorption of 2-CdA on days 1 and 5 were estimated by fitting a three-compartment open model with first-order input to the oral data using PCNONLIN, version 4.2. The following four differential equations were used to describe the model:

$$\begin{aligned} \frac{dC_p}{dt} &= [K_a \cdot X_a - (K_{10} + K_{12} + K_{13}) \cdot C_p \cdot V_c + K_{21} \cdot X_2 + K_{31} \cdot X_3] / V_c \\ \frac{dX_2}{dt} &= K_{12} \cdot C_p \cdot V_c - K_{21} \cdot X_2 \\ \frac{dX_3}{dt} &= K_{13} \cdot C_p \cdot V_c - K_{31} \cdot X_3 \\ \frac{dX_a}{dt} &= K_a \cdot X_a \end{aligned}$$

where  $C_p$  is the plasma concentration, and  $X_a$ ,  $X_2$ , and  $X_3$  are amounts of drug at the absorption site (the gastrointestinal tract) and tissue compartments 2 and 3, respectively. Macro constants estimated for individual subjects from the day 5 IV data were used in the model fitting.

For the model fitting of day 5 oral data, plasma concentrations of 2-CdA were corrected for the contribution of predose 2-CdA concentrations by subtracting  $C_0 \cdot e^{-\gamma t}$  from the 2-CdA concentration at each time point, where  $C_0$  is the 2-CdA plasma concentration at the time immediately before dosing on day 5,  $\gamma$  is the terminal-phase elimination rate constant determined from the day 5 IV data, and  $t$  is the time postdosing on day 5.

Plasma 2-CdA concentration-time profiles after oral administration of 0.28 mg/kg/d for 5 consecutive days for individual patients were simulated using average  $K_a$  values and individual macro constants estimated from the day 5 IV data.

## RESULTS

### Patient Demographics

Eleven patients, six with solid tumors and five with hematologic malignancies, entered the study (Table 1).

Table 1. Patient Characteristics

Characteristic	Total
No. of patients	11
Sex (male:female)	6:5
Age, years	
Median	59
Range	38-68
Prior chemotherapy	
No. of regimens	
0	0
1-2	6
3-4	4
≥ 5	1
Malignancy	
Nonhematologic	
Colon	3
Ovary	1
Biliary	1
Kidney	1
Hematologic	
AML	1
CML, blast crisis	1
Lymphoma	2
LGL leukemia	1

Abbreviations: AML, acute myeloid leukemia; CML, chronic myeloid leukemia; LGL, large granular lymphocyte.

Ten patients completed treatment cycle 1 (oral 2-CdA) and cycle 2 (IV 2-CdA), while one patient with refractory acute myeloid leukemia completed only cycle 1. This patient had progressive disease and did not receive cycle 2. All 11 patients were evaluated for toxicity, but only the 10 patients who completed cycles 1 and 2 were included in the pharmacokinetic analysis.

#### Noncompartmental Data Analysis

Mean plasma 2-CdA concentrations as a function of time are shown in Fig 1. Mean model-independent pharmacokinetic parameters are listed in Table 2. There was no significant accumulation in  $C_{max}$  (day 5 v day 1) for both IV and oral administration of 2-CdA. The F values observed on day 1 and day 5 (~ 37%) were similar. The  $C_{max}$  occurred approximately 1 hour after oral administrations and 1.86 hours after IV dosing. At half the IV dose, the  $C_{max}$  values after oral administrations were similar to those following the 2-hour IV infusions. Intersubject variabilities (reflected by the CV values) in  $C_{max}$  and  $AUC_{(0-24)}$  values were comparable between IV and oral doses on days 1 and 5.

#### Compartmental Data Analysis

The “goodness-of-fit” of the three-compartment open-model to the day 5 IV concentration-time data was excel-

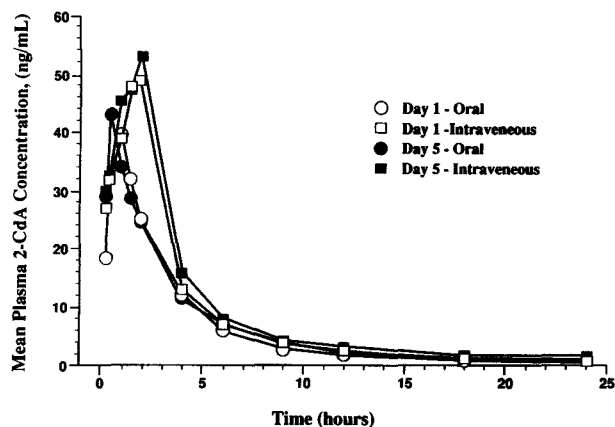


Fig 1. Mean 2-CdA plasma concentrations from 0 to 24 hours after oral administration of 0.28 mg/kg/d on days 1 and 5, and IV infusion of 0.14 mg/kg/d on days 1 and 5.

lent. The correlations of the model fitting were more than 0.96 and the Akaike Information Criterion<sup>19</sup> and Schwarz Criterion<sup>20</sup> criteria were less than 50 for all patients. Macro constants and pharmacokinetics constants estimated from the model fitting are listed in Table 3. These macro constants were used to simulate the concentration-time profiles after 5 consecutive days of IV and oral administrations. There was good agreement between the observed and simulated plasma concentration-time profiles for all patients, which indicates that the disposition of 2-CdA in humans can be described by a three-compartment open model. Observed and simulated plasma concentration-time profiles of 2-CdA for a representative patient are shown in Fig 2.

#### Toxicity

As for hematologic toxicity, among 11 patients who received oral 2-CdA, three experienced grade 3 or 4 neu-

Table 2. Model-Independent Pharmacokinetic Parameters

Parameter	IV Infusion		Oral Administration	
	Mean ± SD	CV (%)	Mean ± SD	CV (%)
$T_{max}$ (hours)				
Day 1	1.86 ± 0.25	13.4	1.08 ± 0.40	37.2
Day 5	1.83 ± 0.37	20.5	0.73 ± 0.45	61.8
$C_{max}$ (ng/mL)				
Day 1	53.9 ± 19.9	36.9	42.4 ± 19.0	44.8
Day 5	55.8 ± 21.8	39.1	45.3 ± 16.7	37.0
$AUC_{0-24}$ (ng · h/mL)				
Day 1	199 ± 70	35.1	146 ± 56	38.5
Day 5	225 ± 94	42.0	153 ± 46	30.1
F (%)				
Day 1			37.2 ± 9.8	26.3
Day 5			36.7 ± 9.0	24.5

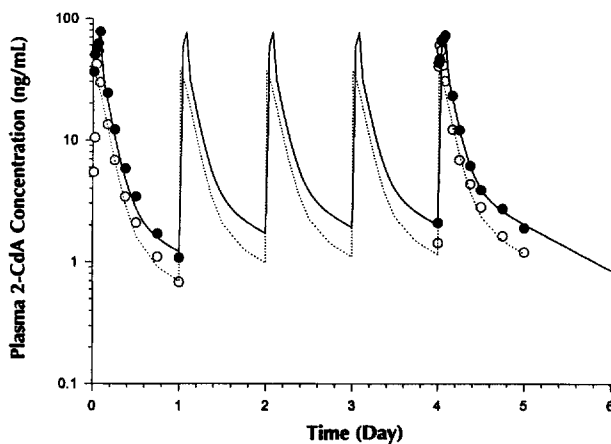
**Table 3. Macro Constants and Pharmacokinetic Parameters Estimated From Fitting of Data to a Three-Compartment Open Model**

Macro Constants	Mean $\pm$ SD	CV
$K_{10}$ (hours <sup>-1</sup> )	3.68 $\pm$ 3.01	81.8
$K_{12}$ (hours <sup>-1</sup> )	8.42 $\pm$ 7.92	94.2
$K_{21}$ (hours <sup>-1</sup> )	1.19 $\pm$ 1.43	119.6
$K_{13}$ (hours <sup>-1</sup> )	1.24 $\pm$ 1.09	87.8
$K_{31}$ (hours <sup>-1</sup> )	0.065 $\pm$ 0.030	46.2
$T_{1/2\alpha}$ (hours <sup>-1</sup> )	0.25 $\pm$ 0.41	165.5
$T_{1/2\beta}$ (hours <sup>-1</sup> )	3.38 $\pm$ 3.99	118.1
$T_{1/2\gamma}$ (hours <sup>-1</sup> )	16.4 $\pm$ 7.1	43.1
AUC <sub>0-∞</sub> (ng·h/mL)	200 $\pm$ 83	41.6
Clearance (L/h/kg)	0.839 $\pm$ 0.396	47.1
$V_c$ (L/kg)	0.529 $\pm$ 0.460	86.9
$V_{ss}$ (L/kg)	7.72 $\pm$ 6.23	80.7
$K_0$ estimated on day 1 (hours <sup>-1</sup> )	1.36 $\pm$ 1.46	107.7
$K_0$ estimated on day 5 (hours <sup>-1</sup> )	2.09 $\pm$ 2.36	113.0
Overall mean $K_0$ (hours <sup>-1</sup> )	1.72 $\pm$ 1.95	113.0

Abbreviation:  $V_c$ , apparent volume of distribution in the central compartment.

tropenia and one with baseline anemia required RBC transfusional support (Table 4). Of 10 patients who received IV infusions of 2-CdA, four experienced grade 3 or 4 neutropenia and one, also with preexisting anemia, required RBC transfusions.

Regarding infectious toxicities, the patient with grade 4 neutropenia following oral administration of 2-CdA had refractory acute myeloid leukemia and the neutropenia was associated with enterococcal bacteremia. Following IV 2-CdA, one patient with grade 3 neutropenia and a clear chest x-ray received oral antibiotics for bronchitis. One patient with non-Hodgkin's lymphoma received IV



**Fig 2.** Observed and simulated plasma concentrations after oral administration of 0.28 mg/kg/d (○ and ----, respectively) or IV infusion of 0.14 mg/kg/d (● and —, respectively) for 5 days for a representative subject.

**Table 4. Hematologic Toxicity**

Hematologic Parameter	Maximum ECOG Toxicity Grade				Total No. of Patients
	3*	4*	3†	4†	
Neutropenia	2	1	3	1	5
Thrombocytopenia	0	0	0	0	0
Anemia	1	0	1	0	2

\*Cycle 1, oral (n = 11).

†Cycle 2, IV (n = 10).

antibiotics for pneumonia unassociated with significant neutropenia.

Two patients, one with metastatic hypernephroma and the other with metastatic ovarian carcinoma, developed deep venous thromboses. No patients had alopecia, gastrointestinal, pulmonary, cardiac, renal, or neurologic toxicities.

### Responses

None of six patients with solid tumors responded. Of five patients with hematologic malignancies, two responded. One patient with chronic myeloid leukemia in blast crisis had a more than 50% sustained reduction in spleen size and peripheral blood blast count after receiving a total of six cycles of 2-CdA. He remains alive 15 months after first receiving 2-CdA. One patient with T-cell large granulocyte lymphocyte leukemia had a partial response of 5+ months (> 50% reduction in spleen size and an absolute neutrophil count > 1.0 × 10<sup>9</sup>/L) following five courses of 2-CdA.<sup>21</sup>

### DISCUSSION

Prolonged exposure of resting peripheral-blood lymphocytes to 2-CdA in vitro resulted in greater lymphocytotoxicity than did brief incubations,<sup>18</sup> which led to the selection of a continuous IV infusion schedule for the initial clinical trials. The 2-CdA dose of 0.09 to 0.10 mg/kg/d by continuous IV infusion for 7 days has been previously demonstrated to be an effective phase II dose.<sup>22</sup> Pharmacokinetic studies have shown high concentrations and prolonged intracellular retention of 2-chlorodeoxyribonucleotides in chronic lymphocytic leukemia cells following bolus administration of 2-CdA.<sup>23</sup> The 2-hour bolus method of 2-CdA administration was developed in an attempt to facilitate the outpatient administration of 2-CdA and was shown to be effective in 90 patients with alkylator-failed chronic lymphocytic leukemia, when a comparable total cumulative dose of bolus 2-CdA (21 patients) to infusional 2-CdA (69 patients) was compared (0.1 mg/kg/d by continuous IV infusion for 7 days being dose-equivalent to 0.14 mg/kg/d by 2-hour bolus for 5

days), the response rates and toxicities of the two regimens were similar.<sup>7</sup> In a study conducted by Liliemark et al,<sup>15</sup> the *F* value of 2-CdA in three patients given 2-CdA at 0.14 mg/kg orally dissolved in phosphate-buffered saline was 48% ± 8% (mean ± SD), whereas in seven patients who received 0.28 mg/kg orally it was 55% ± 17%. In support of the hypothesis that the oral administration of 2-CdA could supersede IV infusions if the dose was doubled, of 17 patients with untreated chronic lymphocytic leukemia treated with oral 2-CdA, seven (41%) achieved a complete response and five (29%) a partial response.<sup>24</sup>

In this study, there were no apparent differences in *F* values observed after multiple dosing on day 1 and day 5. The *F* values reported here (~ 37%) are lower than those reported by Liliemark et al<sup>15</sup> (~ 55%), who gave 2-CdA as a 2-hour IV infusion, subcutaneous injection, and an oral dose over 3 consecutive days with no washout periods between drug administrations. These higher *F* values could be due to residual drug from previous dose(s). We documented no significant accumulation in *C*<sub>max</sub> for both oral and IV 2-CdA administration and comparable intersubject variabilities (CVs) in *C*<sub>max</sub> and AUC<sub>(0-24)</sub> values between oral and IV, on days 1 and 5.

The apparent volume of distribution of the central compartment ranged from 0.065 to 0.73 L/kg (mean, 0.53 L/kg), which indicates that the distribution space of 2-CdA in the central compartment ranged from plasma volume to total-body water. This suggests a rapid distribution of 2-CdA into tissue cells. The large *V*<sub>ss</sub> (range, 2.93 to 20.85 L/kg) also indicates extensive distribution of 2-CdA into tissues. The *t*<sub>1/2</sub> for the terminal elimination phase of the concentration-time curve ranged from 7.5 to 31.8 hours.

The excellent agreement between the observed and simulated concentration-time profiles after oral and IV administration validates the three-compartment open model for drug distribution. This indicates that the absorption and disposition characteristics of oral 2-CdA are linear and predictable with the dosing regimen used in this study.

The intersubject variability reported after oral adminis-

trations of 2-CdA was similar to that after IV dosing, and the *F* value was consistent between days 1 and 5. These results should be interpreted cautiously, since pharmacokinetic determinations were conducted under well-controlled conditions. 2-CdA was administered in the fasting condition and stomach acid secretion was suppressed by omeprazole. Concentration-time profiles after oral administration in noninvestigative clinical settings could be substantially different from those observed in this study due to the effects of stomach acid and food. Any clinical application of this route of administration will thus need to be accompanied by adherence to these conditions. However, other investigators have demonstrated that the *F* value of oral 2-CdA was not enhanced by protection against the gastric acid environment using omeprazole.<sup>25</sup>

It should be pointed out that 2-CdA must first be intracellularly phosphorylated by deoxycytidine kinase to its triphosphate derivative, 2-chlorodeoxyadenosine triphosphate, to exert its lymphocytotoxic actions,<sup>26</sup> and that the relationship between plasma 2-CdA concentrations and intracellular 2-chlorodeoxyadenosine triphosphate concentrations remains to be established. Also, the extent of formation of 2-chloroadenine, an important catabolic product of 2-CdA detected in the plasma of patients treated with orally administered 2-CdA,<sup>18</sup> indicates that a substantial part of the oral dose may be deglycosylated before absorption, which may partly explain why the *F* value of 2-CdA was only 37%.<sup>27</sup> Data on the formation of 2-chloroadenine in the gastrointestinal tract and the oral absorption, safety, and pharmacologic activities of 2-chloroadenine will need to be more fully elucidated before the oral route of administration of 2-CdA is used.

#### ACKNOWLEDGMENT

We thank Richard Nelson, from the R.W. Johnson Pharmaceutical Research Institute, for help in the preparation of the study protocol, Mary-Helen Hader for data collection, and the nursing staff of the General Clinical Research Center of Scripps Clinic for help in completing the study.

#### REFERENCES

1. Seto S, Carrera CJ, Kubota M, et al: Mechanism of deoxyadenosine and 2-chlorodeoxyadenosine toxicity to nondividing human lymphocytes. *J Clin Invest* 75:377-383, 1985
2. Seto S, Carrera CJ, Wasson DB, et al: Inhibition of DNA repair by deoxyadenosine in resting human lymphocytes. *J Immunol* 136:2839-2843, 1986
3. Piro LD, Carrera CJ, Carson DA, et al: Lasting remissions in hairy cell leukemia induced by a single infusion of 2-chlorodeoxyadenosine. *N Engl J Med* 322:1117-1121, 1990
4. Saven A, Piro L: Newer purine analogues for treatment of hairy cell leukemia. *N Engl J Med* 330:691-697, 1994
5. Estey EM, Kurzrock R, Kantarjian HM, et al: Treatment of hairy cell leukemia with 2-chlorodeoxyadenosine (2-CdA). *Blood* 79:882-887, 1992
6. Tallman MS, Hakimian D, Variakojis D, et al: A single cycle of 2-chlorodeoxyadenosine results in complete remission in the majority of patients with hairy cell leukemia. *Blood* 9:2203-2209, 1992
7. Saven A, Carrera CJ, Carson DA, et al: 2-Chlorodeoxyadenosine treatment of refractory chronic lymphocytic leukemia. *Leuk Lymphoma* 5:133-138, 1991 (suppl)
8. Juliusson G, Liliemark J: High complete remission rate from 2-chloro-2'-deoxyadenosine in previously treated patients with B-

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.