Pharmacokinetics of Cladribine in Plasma and Its 5'-Monophosphate and 5'-Triphosphate in Leukemic Cells of Patients with Chronic Lymphocytic Leukemia

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ABSTRACT

The pharmacokinetic parameters of cladribine (CdA) in patient plasma and its intracellular nucleotides CdA 5'-monophosphate (CdAMP) and CdA 5'-triphosphate (CdATP) were delineated in circulating leukemia cells in 17 patients with chronic lymphocytic leukemia, after the last dose intake and up to 72 h thereafter. Patients were treated with 10 mg/m² CdA p.o. on 3 consecutive days. A novel and specific ion-pair liquid chromatographic method, which separates the intracellular CdA nucleotides, was used. The area under the concentration versus time curve (AUC) of CdAMP in leukemia cells was generally higher (median, 47 μmol/liter-h) than the AUC of CdATP (median, 22 μmol/liter-h); however, in some patients (3 of 17), the reverse relationship was seen. The median ratio between the AUC values for CdATP and CdAMP was 10 h. The median half-life (t½) of CdATP was 15 h, and that of CdATP was 60 h. A significant correlation was found between the maximum plasma CdA and cellular CdAMP concentrations (r = 0.56, P = 0.02). There was no correlation between the AUC values of cellular CdAMP and CdATP (r = 0.224, P = 0.55). No correlation was found between deoxycytidine kinase activity and intracellular pharmacokinetic parameters of CdAMP or CdATP. The response to treatment was not significantly related to intracellular concentration of CdAMP or active metabolite CdATP. There is great heterogeneity among patients in terms of AUC and t½ of CdAMP and CdATP. Furthermore, the results emphasize the differences between the pharmacokinetics of plasma CdA and those of the metabolites in circulating leukemic cells.

INTRODUCTION

The antimetabolite 2-chloro-2'-deoxyadenosine (CdA3 or Leustatin) is a purine analogue that is resistant to adenosine deaminase due to protonation at the N-7 position (1). In dividing cells, CdA is incorporated into DNA and arrests cells in S phase (2). CdA also inhibits ribonucleotide reductase (3), thus causing an imbalance in the intracellular pool of deoxyribonucleotides. In nondoning cells, CdA causes an accumulation of DNA strand breaks, which activates poly(ADP) ribosylation, leading to depletion of NAD and apoptosis (4, 5).

CdA is the drug of choice for HCL (6), with about an 85% complete response. It is also a promising drug for the treatment of other lymphoproliferative disorders, such as CLL (7–9), low-grade non-Hodgkin’s lymphoma (10), and Waldenström’s macroglobulinemia (11). CdA is also effective in acute myeloblastic leukemia (12, 13), Langerhans cell histiocytosis (14), multiple sclerosis, and other autoimmune diseases (15, 16).

CdA is a prodrug and intracellular phosphorylation is needed for cytotoxic effect. Interindividual variability in intracellular phosphorylation may explain differences in response to the treatment. Investigation of the cellular pharmacokinetics of the active metabolites is, therefore, warranted. The metabolic pathways of CdA include degradation to CAde (17), an apparently inactive metabolite (18), and intracellular phosphorylation of CdA by dCK to CdAMP (19) and, further, to CdATP by relatively abundant nucleotide kinases. In contrast to other nucleoside analogues, the phosphorylation of CdA by dCK to its 5'-monophosphate, CdATP, is not the rate-limiting step in the anabolism of the CdA to CdATP. CdATP is generally considered to be responsible for the cytotoxic effects of CdA. However, previous pharmacokinetic studies suggest that there is a direct relationship between plasma pharmacokinetics and the clinical outcome in HCL (20).

The cellular pharmacokinetics of total CdA nucleotides were described previously (21). In that study, the concentrations

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3 The abbreviations used are: CdA, cladribine; HCL, hairy cell leukemia; CLL, chronic lymphocytic leukemia; CAde, 2-chloroadenine; dCK, deoxycytidine kinase; CdAMP, CdA 5'-monophosphate; CdATP, CdA 5'-triphosphate; HPLC, high-performance liquid chromatography; AUC, area under the concentration versus time curve; CI, confidence interval.
of the total CdA nucleotides were measured indirectly from the concentrations of the parent nucleoside, CdA, following dephosphorylation by treating CdA nucleotides with alkaline phosphatase. The cellular kinetics of CdA metabolites (specifically, CdAMPs and CdATPs) have not been determined previously in vivo.

Here, we describe the intracellular pharmacokinetics of CdAMP and CdATP during the treatment of CLL, with a comparison to the plasma pharmacokinetics using a specific ion-pair HPLC method. A preliminary report of part of this work was reported elsewhere in abstract form (22).

### PATIENTS AND METHODS

#### Chemicals and Reagents.
CdATP, synthesized by Sierra Bioresearch (Tucson, AZ), was provided by Dr. William Plunkett (M. D. Anderson Cancer Center, Houston, TX). CdA and CAde were synthesized by Dr. Zygmunt Kazimierczuk at the Foundation for the Development of Diagnostics and Therapy (Warsaw, Poland). The molar absorbivities were 15,000 and 12,600 absorbtivity units/mol for CdA and CAde, respectively, at 264 nm (pH 7.0). Guaneran was generously donated by Dr. Gertrude Elion (Wellcome Foundation, Research Triangle Park, NC). Triethylamine was purchased from Fluka (Buchs, Switzerland), and Lymphoprep was purchased from Nycomed (Oslo, Norway). Other compounds were of analytical grade and purchased from Sigma Chemical Co. (St. Louis, MO).

#### Patients and Treatment.
Seventeen patients with (B-cell) CLL participated in the study, having given their informed consent prior to initiation of the study (Table 1). The study was approved by the local Ethics Committee at the Karolinska Institute (Dnr 94:369) and the Swedish Medical Products Agency (Dnr 151:1603/94). CdA was administered over 3 consecutive days. The dose for i.v. (2-h infusion) administration was 5 mg/m². The corresponding p.o. dose was 10 mg/m², administered after overnight fasting. The solutions (2 mg/ml) were taken with 150 ml of water. No food was allowed until 2 h after dosage. Patients receiving the CdA treatment in the study were required to have normal renal and hepatic function. Response to treatment was evaluated according to guidelines for clinical protocols for CLL, as recommended by the National Cancer Institute (23). Responders are patients who had partial or complete remissions, and nonresponders are patients who had stable or progressive disease.

#### Blood Sampling.
Venous blood samples (10 ml) were collected from an indwelling catheter into heparinized Venoject tubes before drug intake at the following time points: before and 1, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, 60, and 72 h after dosing on day 3. In the first two patients, three additional blood samples were also taken at 0.25, 1.5, and 20 h after dosing. The blood was stored on ice. The plasma and leukemic cells were isolated within 6 h after sampling and frozen immediately at −20°C. The analyses were performed within 2 months for plasma and within 3 weeks for cellular CdA metabolite measurements.

#### Leukemic Cell Isolation.
Mononuclear cells were isolated by Ficoll-Hypaque density centrifugation. After separation on Lymphoprep and washing with PBS, the cell pellet was dissolved in 2 ml of ice-cold distilled water. One ml of 2.7% NaCl was added, and after 30 s, the volume was adjusted to 50 ml with PBS. The number of cells in the samples and the median cell volume of the samples analyzed were determined by a Coulter Multisizer (Coulter Electronics, Luton, United Kingdom).

#### Determination of CdA, CAde, and CdA Nucleotides.
A previously published (17) reversed-phase HPLC method was used to quantitate CdA and CAde in plasma. CdA and CAde were determined at 265 nm, with a limit of quantitation of 1 nM using 1 ml of plasma.

CdA nucleotides were extracted from leukemic cells by a previously described HPLC method (24). In brief, a 200-μl volume of ice-cold 0.4 M perchloric acid containing 0.08 M triethylammonium phosphate was added to the cell pellet (1 × 10³-3 × 10⁸), mixed on a vortex mixer, and brought to pH 6.2 by addition of 100 µl of ice-cold 1.2 M potassium hydroxide-0.4 M ammonium dihydrogenphosphate. The supernatant was collected after vortex mixing and centrifugation at 14,500 × g for 5 min at 4°C. A 90-μl aliquot was injected onto the HPLC column directly, or the sample was stored at −20°C until analysis. The column was an Ultrasphere ODS (250 × 4.6 mm; 5 μm), purchased from Beckman Instruments (Fullerton, CA) and equipped with the Guard-Pak precolumn (μBondapak C18; Millipore, Milford, MA). The mobile phase consisted of triethylammonium phosphate buffer (0.08 M, pH 6.1) and methanol (89:11, v/v). The elution was carried out at flow rates of 1.5 and 1.8 ml/min, respectively, at 265 nm and at the ambient temperature (22°C). The temperature of the autosampler was maintained at 8°C. The concentration of the CdA nucleotides was measured by comparing the peak area of the CdAMP and CdATP concentrations obtained with those of the standard substance, CdATP.

#### Measurement of dCK.
dCK activities were measured in extracts of leukemic cells according to a previously published procedure (25) using CdA as a substrate. The dCK activities were expressed as pmol/mg of cellular protein/min (pmol/mg/min).

#### Pharmacokinetic Variables.
Pharmacokinetic variables were calculated for each subject from the plasma and cell
concentrations after a single dose of p.o. CdA, using a commercially available program, SIPHAR (Version 4.0; Siphar Société Simed, Creteil, France). The maximum concentration ($C_{\text{max}}$) and the time to reach $C_{\text{max}}$ ($T_{\text{max}}$) were obtained from observed experimental values. The initial and elimination half-lives ($t_{1/2}$) were calculated using the pharmacokinetic model, fitted by means of weighted least squares analysis by two- or three-compartment modeling. Parameters producing the smallest log likelihood, the Akaike criterion, and the best fit of the data points were accepted. The AUCs were calculated from the trough level (immediately before administration of CdA) to 24 h using the linear trapezoidal rule.

The p.o. bioavailability of CdA in blood was studied in two patients. These two patients were treated first by CdA with a 2-h infusion (5 mg/m²) on day 1, and then after 24 h, they were treated with p.o. CdA (10 mg/m²). The residual area ($\text{AUC}_{24-\infty}$) from 2-h i.v. infusion was subtracted from the AUC$_{0-24}$ of p.o. administration on day 2 to compensate for the spillover from the previous dose. The bioavailability ($F$) of CdA and CdA nucleotides was calculated for each patient as: $F = (\text{AUC}_{0-24} \text{ p.o.} \times \text{i.v. dose})/ (\text{AUC}_{0-\infty} \text{ i.v.} \times \text{p.o. dose})$.

### Statistical Evaluation
Data were expressed as medians and 95% CIs due to the skewness in the distribution of some of the data. The correlations between clinical outcome and dCK and plasma and cellular pharmacokinetics were based on the Mann-Whitney rank sum test. The correlation between plasma and cellular concentrations was analyzed by means of Pearson’s correlation coefficient and linear regression analysis. Statistical calculations were done using StatView software (Abacus Concepts, Berkeley, CA). A $P$ of $<0.05$ was regarded as statistically significant.

### RESULTS

**Plasma Pharmacokinetics.** The medians and 95% CIs of plasma pharmacokinetic parameters after p.o. administration of CdA in 17 patients with CLL are summarized in Table 2. The pharmacokinetic profile of CdA was best described by two-compartment modeling with a median distribution $t_{1/2}$ of 1.3 h, followed by a slow elimination $t_{1/2}$ of 21.1 h. This is illustrated in Fig. 1, in which the median CdA, Cade, and cellular CdA and CdATP concentrations versus time are presented. The overall pharmacokinetics of CdA are in agreement with previously reported studies.

**Cellular Pharmacokinetics.** The CdA nucleotides accumulated rapidly in the leukemic cells, and the $C_{\text{max}}$ of CdAMP and CdATP after p.o. administered CdA were more than 85 and 40 times, respectively, higher than plasma CdA. In most patients, CdAMP could be detected in leukemic cells for up to 72 h, and CdATP could be detected up to 48 h after the last CdA dose. The AUC of CdAMP in leukemic cells was generally

### Table 2 Kinetic parameters of CdA in plasma and CdAMP and CdATP in leukemic cells after administration of a single p.o. dose of CdA in patients with CLL

<table>
<thead>
<tr>
<th>Compound</th>
<th>All patients$^a$</th>
<th>CdAMP &gt; CdATP$^b$</th>
<th>CdATP &gt; CdAMP$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>95% CI</td>
<td>Median</td>
</tr>
<tr>
<td>CdA</td>
<td>$\text{AUC}_{0-24}$ ($\mu$mol/liter $\cdot$ h)</td>
<td>0.541 (0.494–0.797)</td>
<td>0.534 (0.494–0.797)</td>
</tr>
<tr>
<td></td>
<td>$T_{\text{max}}$ (h)</td>
<td>1.0 (0.9–1.7)</td>
<td>1.0 (0.9–1.7)</td>
</tr>
<tr>
<td></td>
<td>$C_{\text{max}}$ ($\mu$mol/liter)</td>
<td>0.107 (0.086–0.140)</td>
<td>0.112 (0.086–0.140)</td>
</tr>
<tr>
<td></td>
<td>Distribution $t_{1/2}$ (h)</td>
<td>1.3 (1.1–2.7)</td>
<td>1.4 (1.1–2.7)</td>
</tr>
<tr>
<td></td>
<td>Elimination $t_{1/2}$ (h)</td>
<td>21.1 (18.2–44.8)</td>
<td>29.9 (22.3–49.4)</td>
</tr>
<tr>
<td>CdAMP</td>
<td>$\text{AUC}_{0-24}$ ($\mu$mol/liter $\cdot$ h)</td>
<td>47.0 (35.1–114.6)</td>
<td>75.5 (56.2–104.8)</td>
</tr>
<tr>
<td></td>
<td>$T_{\text{max}}$ (h)</td>
<td>2.0 (1.1–4.1)</td>
<td>2.0 (1.1–4.1)</td>
</tr>
<tr>
<td></td>
<td>$C_{\text{max}}$ ($\mu$mol/liter)</td>
<td>4.9 (4.9–12.6)</td>
<td>7.9 (5.6–11.1)</td>
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<td></td>
<td>Initial $t_{1/2}$ (h)</td>
<td>0.9 (0.8–2.2)</td>
<td>0.9 (0.8–2.2)</td>
</tr>
<tr>
<td></td>
<td>Elimination $t_{1/2}$ (h)</td>
<td>14.6 (9.3–18.0)</td>
<td>12.0 (8.6–15.4)</td>
</tr>
<tr>
<td>CdATP</td>
<td>$\text{AUC}_{0-24}$ ($\mu$mol/liter $\cdot$ h)</td>
<td>21.7 (17.2–43.3)</td>
<td>21.5 (16.9–27.1)</td>
</tr>
<tr>
<td></td>
<td>$T_{\text{max}}$ (h)</td>
<td>2.0 (1.8–3.9)</td>
<td>2.0 (1.8–3.9)</td>
</tr>
<tr>
<td></td>
<td>$C_{\text{max}}$ ($\mu$mol/liter)</td>
<td>3.5 (2.3–4.8)</td>
<td>3.7 (2.5–4.9)</td>
</tr>
<tr>
<td></td>
<td>Initial $t_{1/2}$ (h)</td>
<td>0.8 (0.6–2.9)</td>
<td>0.7 (0.5–2.1)</td>
</tr>
<tr>
<td></td>
<td>Elimination $t_{1/2}$ (h)</td>
<td>9.7 (5.3–15.7)</td>
<td>8.8 (4.9–12.6)</td>
</tr>
</tbody>
</table>

$^a$ Medians and 95% CIs of pharmacokinetic parameters in all patients ($n = 17$).
$^b$ Medians of pharmacokinetic parameters in patients ($n = 14$) where the level of the CdAMP was higher than that of CdATP.
$^c$ Medians of pharmacokinetic parameters in patients ($n = 3$) showing a reversed relationship of the CdATP to CdAMP concentration described in footnote b.

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Fig. 1 The median concentrations of CdA (△) and its deglycosylated product, CAd (○), in plasma and of CdA nucleotides CdAMP (●) and CdATP (■) in leukemic cells in 17 patients treated with p.o. CdA.
higher (median, 47 μmol/liter·h) than the AUC of CdATP (median, 22 μmol/liter·h). However, in some patients (3 of 17), the reverse relationship was seen. The median ratio between the AUC for CdATP and for CdAMP was 0.60 (95% CI, 0.4–1.0). The median initial $t_{1/2}$s were 0.9 and 0.8 h for CdAMP and CdATP, respectively, whereas the terminal phases had median $t_{1/2}$s of 14.6 and 9.7 h, respectively (Table 2). The concentration of the 5′-diphosphate was much lower, and in most patients, it was undetectable. There was no interference with CdA or CdA nucleotides in the chromatogram when CCRF-CEM or patient cells were exposed to 10 μM CAde for 2 h (data not shown).

In two of the patients, the pharmacokinetic parameters of CdA nucleotides after 10 mg/m² CdA p.o. were compared with those after 2-h i.v. infusions (5 mg/m²). The formation and retention of CdA nucleotides by circulating cells in one of the patient is illustrated in Fig. 2. The AUC$_{0-24}$s of CdA total nucleotides after a p.o. dosing were 99 and 78 μmol/liter·h, and those after 2-h infusion were 130 and 114 μmol/liter·h, respectively, in the two patients. The plasma p.o. bioavailabilities of CdA were 61 and 55% in the two patients, whereas the amounts of CdATP formed in circulating lymphocytes after p.o. dose were 57 and 33%, respectively (33 and 36% of CdAMP; compensated for dose), of those after i.v. dose.

The statistical analysis of the data failed to show any correlation between plasma CdA and cellular CdATP kinetics at $C_{\text{max}}$ (Fig. 3, bottom; $r = 0.22, P = 0.40$), as well as AUC ($r = 0.28$; data not shown). There was, however, a weak but significant correlation between the $C_{\text{max}}$ of CdA in plasma and the $C_{\text{max}}$ of CdAMP (Fig. 3, top; $r = 0.56, P = 0.02$). The response to the treatment was not significantly related to intracellular concentration of CdAMP or the active metabolite CdATP.

**dCK Levels in CLL.** dCK levels were determined prior to treatment with CdA in 16 patients. The median level of dCK was 270 pmol/mg/min (95% CI, 217–435 pmol/mg/min). No correlation was found between dCK activity alone and intracellular pharmacokinetic parameters of CdAMP or CdATP or clinical response in these patients.

**DISCUSSION**

The newer purine analogues, such as CdA, represent a promising new family of anticancer agents because of their unique mechanism of action and clinical activity in lymphoproliferative disorders. As is often the case in cancer chemotherapy, the response to treatment is heterogeneous, with long-lasting complete remissions in some cases and progression during treatment in others. The difference in plasma and cellular pharmacokinetics of CdA may partly explain such differences in the clinical activity of the drug. We have previously shown that there is a weak but significant correlation between the plasma AUC of CdA and the clinical response in HCL (20).

Here, we present a pharmacokinetic study comparing CdA along with its catabolite, CAde, in plasma with the active metabolites CdAMP and CdATP in leukemic cells.

Our results concerning the pharmacokinetics of CdA in plasma were in good agreement with previously published data (26–31). Differences in the terminal half-lives for CdA between
studies probably reflect differences in sampling time and pharmacokinetic calculations.

While phosphorylation of CdA is recognized as the activation process, deglycosylation causes deactivation by acidic hydrolysis in the stomach or enzymatic hydrolysis by intestinal bacteria or as a first-pass effect in the liver after p.o. administration (32, 33). CdA is phosphorylated intracellularly to CdAMP by dCK (19) and deoxyguanosine kinase (34). Whereas dCK is a cytoplasmic enzyme, deoxyguanosine kinase is located in mitochondria, and its importance for the bioactivation of CdA is not clear. CdA 5'-diphosphate and CdATP are formed through phosphorylation of CdAMP by nucleoside monophosphate kinase and nucleoside diphosphate kinase.

The great interpatient variability of the AUC of CdAMP is the product of dCK activity and the CdA concentration, along with the activity of degradation of CdAMP in leukemic cells. The dCK activity has been shown to correlate with the clinical response in CLL in two independent studies (35, 36). However, the truly active metabolite is probably the CdATP, whereas the monophosphate only represents an intermediate step in the bioactivation of CdA. There was great interpatient variability in CdATP concentrations of tumor cells expressed as AUC, ranging from undetectable to 91 μmol/liter·h, and we found no correlation between cellular CdAMP and CdATP levels in the patient cells. The reason for the AUC of CdATP being lower than that of CdAMP could be that there is a low capacity of the phosphorylating enzymes or a higher rate of degradation of CdATP and that the equilibrium of the two processes determines the intracellular concentration level. The shorter t1/2 of CdATP as compared to CdAMP suggests that degradation is the most important of these processes. Furthermore, although a majority of the patients studied had a larger AUC for CdATP than for CdATP, the opposite was found in three cases. When the intracellular pharmacokinetics from these 3 patients were compared to those of the other 14 patients, it was revealed that the t1/2 of CdATP was substantially, although not statistically, longer (Table 2). There was also a trend toward a longer t1/2 of the CdAMP in this group. This also supports the conclusion that the intracellular t1/2 is the most important determinant for the intracellular CdATP concentration. This emphasizes the importance of determining the intracellular metabolites specifically.

The t1/2 of CdAMP (14.6 h) and CdATP (9.7 h) were considerably shorter in this study than they were in a previous publication (>30 h; Ref. 21), in which the total CdA nucleotide concentration in leukemic cells was determined. This difference probably reflects differences in the sensitivity of the assays used and the duration of sampling (2–3 versus 7 days).

There was no clear-cut relationship between the plasma levels of CdA and the intracellular concentration of the active metabolites. A weak correlation of uncertain significance was seen between the Cmax of CdA in plasma and the Cmax of CdAMP in leukemic cells. In a larger cohort of patients, a weak correlation was also seen between the AUCs of plasma CdA and total CdA nucleotides when differences in dCK activity were compensated for (37).

The dCK activity was measured in 16 (of 17) patients in this study. There was an almost 4-fold difference between the highest (435 pmol/mg/min) and lowest (122 pmol/mg/min) values. There was no correlation between cellular CdATP and the plasma CdA concentrations or dCK activity. It is, therefore, unlikely that the intracellular concentration of active metabolites in the target cells can be accurately predicted by the plasma CdA concentration only or in combination with other parameters.

In this small cohort of patients with heterogeneous medical history, there was no clear-cut relationship between response and pharmacokinetic parameters of CdATP. The dCK activity as well as low cytoplasmic 5'-nucleotidase plus high dCK activities have been shown to correlate with the response to treatment in two independent studies (35, 36). Although patients in these two studies were generally refractory to chemotherapy, the patients in this study were more heterogeneous and differed in disease stage and number of previous chemotherapy treatments. This may be an explanation for the lack of correlation between response to CdA and CdA nucleotide pharmacokinetics or dCK activity. Avery et al. (2) studied the sensitivity of CdA with cell lines of different origins. There was no relationship between the CdA nucleotides and sensitivity to CdA. Furthermore, in a recent investigation, Begleiter et al. (38) did not find a relationship between intracellular accumulation of CdA nucleotides and drug sensitivity in leukemic cells from patients with CLL.

CdATP is an efficient inhibitor of ribonucleotide reductase (39), but the lack of correlation between CdATP and biological response precludes ribonucleotide reductase inhibition as the mechanism of toxicity. However, CdATP can be incorporated into mitochondrial DNA (40), and obviously, due to the compartmentalization of the nucleotide pools, CdATP in whole cells measured here cannot be assumed to represent the concentrations of CdATP available in the mitochondria. Indeed, in a recent report (41), the CdA cytotoxicity to leukemic cell was linked to mitochondrial disturbance of oxidative phosphorylation. Future work should address the question of whether mitochondrial toxicity may be an important part of the biological effects of this class of nucleoside analogues.

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Pharmacokinetics of cladribine in plasma and its 5'-monophosphate and 5'-triphosphate in leukemic cells of patients with chronic lymphocytic leukemia.

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