Phase I and Pharmacokinetic Study of 5-Aza-2'-deoxycytidine (NSC 127716) in Cancer Patients

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ABSTRACT

A phase I trial and pharmacokinetic study of 5-aza-2'-deoxycytidine (5-aza-dCyd) were conducted in 21 patients with advanced solid tumors. The drug was given as three 1-h infusions, separated by intervals of 7 h. Treatment was repeated every 3-6 weeks. Forty-six cycles of 5-aza-dCyd were administered at 7 dose levels ranging from 25 to 100 mg/m² in three infusions. The dose-limiting toxicity was myelosuppression, with a delayed white blood cell nadir, occurring at Day 22. Other toxicities included a mild, reversible elevation of serum creatinine in three patients, minimal nausea and vomiting in six patients, and transient fatigue in three patients. In this study one partial response in a patient with an undifferentiated carcinoma of the ethmoid sinus was observed. Plasma and urinary concentrations of 5-aza-dCyd were measured using a bioassay based on growth inhibition of L1210 leukemia cells in vitro. For 75 and 100 mg/m² given as 1-h infusions, mean peak plasma concentrations of 0.93 and 2.02 μM, respectively, were attained. In seven of nine courses at doses of 25-60 mg/m², plasma 5-aza-dCyd concentration was less than 0.01 μM. In one case at 30 mg/m² and another at 60 mg/m², peak plasma drug concentrations were determined to be 0.244 and 0.409 μM, respectively. Following cessation of the infusion rapid disappearance of drug from plasma was observed with a t₁/₂,α of 1.9 and a t₁/₂,β of 1.7 and 35 min, respectively. High clearance values and a total urinary excretion of less than 1% of the administered dose suggest that 5-aza-dCyd is eliminated rapidly and largely by metabolic processes. For the present schedule studied, a dose of 75 mg/m² in three infusions, every 5 weeks, is recommended for phase II trials in solid tumors.

INTRODUCTION

5-aza-dCyd, an analogue of deoxycytidine whereby carbon five is substituted by nitrogen, has been extensively studied since its synthesis by Pliiml and Sorm in 1964 (1). The mechanism of action of 5-aza-dCyd is believed to result from its incorporation into DNA after its conversion to the nucleotide form by the initial action of deoxycytidine kinase (2). The presence of the analogue base in DNA inhibits DNA methylase (3-5), leading to hypomethylation of DNA which has been associated with activation of gene expression and induction of cell differentiation (6-7). 5-aza-dCyd could be a potential candidate for studies on differentiation inducers in cancer chemotherapy (8). However, it should be noted that 5-aza-dCyd may have mechanisms of cytotoxic action involving DNA damage due to the instability of drug incorporated into DNA (9). D'Incalci et al. (10) have recently demonstrated in L1210 leukemia cells that the incorporation of 5-aza-dCyd into DNA leads to the formation of alkali-labile sites, which were proposed to contain azacytosine residues susceptible to alkali-catalyzed ring opening.

5-aza-dCyd has been shown to possess antineoplastic activity, both in vitro and against the murine leukemias AKR, P388, and L1210 (11-14). Because 5-aza-dCyd is an S-phase-specific agent (15), prolonged exposure of the cells to the drug might be necessary to obtain an optimal cytotoxic effect. This was demonstrated by Covey and Zaharko (16), who investigated the cytotoxicity of 5-aza-dCyd in L1210 cells in vitro and in mice bearing L1210. For both systems the importance of exposure time as a determinant of cell kill was shown in their experiments. The toxicity of 5-aza-dCyd was investigated in mice in different studies (17, 18). Myelosuppression, intestinal mucosa necrosis, and testicular atrophy were apparent from these studies.

A phase I study on 5-aza-dCyd in childhood acute leukemia has been performed by Rivard et al. (19). At doses of 36-80 mg/kg administered as a 36- to 44-h continuous infusion, a potent antileukemic effect was observed, 2 of 9 patients showing a complete remission. Lower doses, shorter exposure time, and administration by bolus i.v. injection were not significantly effective.

We report the results of the first phase I study on 5-aza-dCyd in adults and include an examination of drug pharmacokinetics. An unconventional administration schedule of 3 times a 1-h infusion over 24 h was chosen. In view of the S-phase specificity of 5-aza-dCyd a prolonged drug exposure might be best effected using a continuous infusion (19). However, due to the chemical instability of 5-aza-dCyd (20), possibly inconvenient measures like cooling the infusion fluid or frequent changes of infusion bags would be necessary. The rate of degradation increases with rising temperature and high pH. At pH 7.0, a 10% degradation occurs at temperatures of 4°C, 25°C, and 50°C after 24, 5, and 0.5 h, respectively. A 3 times 1-h infusion schedule appeared to be an acceptable compromise between prolonged exposure and chemical instability.

MATERIALS AND METHODS

Patient Selection. Patient characteristics are shown in Table 1. Twenty-one patients, 15 men and 6 women, ranging in age from 37 to 75 years, were entered into the study. All patients but one had received prior therapy. Eligibility criteria for entry into the study included pathological confirmation of cancer, resistance to conventional therapy (if any), life expectancy of at least 6 weeks, performance status (WHO) of 3 or better, age between 16 and 75 years, no chemotherapy and/or radiotherapy for at least 4 weeks before entry (for nitrosourea, mitomycin C, and extensive radiotherapy, 6 weeks), recovered from toxic effects of prior treatment, adequate bone marrow function (WBC ≥4000/mm³, platelet count ≥100,000/mm³), normal liver function tests (bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase), unless abnormalities could be attributed to metastatic disease, and normal renal function (serum creatinine, <1.3 mg/dl and/or creatinine clearance >60 ml/min). Patients were ineligible for the study in case of central nervous system metastases, evidence of serious nonmalignant disease, and concomitant treatment with corticosteroids. All patients gave written informed consent prior to therapy. Prior to therapy, each patient underwent a comprehensive evaluation including complete history and physical examination and evaluation of measurable disease (if present) by
concentration was 10,000 cells/ml. All assay cultures contained 2-
suspended for 10 min at 3,000 rpm. Plasma was decanted and samples were frozen at —20°C until analysis. Urine samples were also stored at

of 60 /IM, 100 units/ml, and 100 jig/ml, respectively. The plates were placed in a 5% CO2 incubator at 37°C. Cells were counted after 3 days

drawn into 10-ml heparinized tubes prior to therapy; at 15, 30, and 60

weeks; usually treatment was withheld in cases of progressive disease. Cycles were repeated every 3-6

first 3 patients. All subsequent patients received the prescribed dose as

administration by constant infusion. After reconstitution as instructed, the solution of 5-aza-dCyd decomposes by about 10% after 5 h at room

administration for 3-10 nM 5-aza-dCyd was determined by least

squares analysis (r2 = 0.98).

Fig. 1 shows a reproducible log-linear decline in the resulting cell number with addition of 3 to 10 nm 5-aza-dCyd.

A narrow working range required that samples be tested over a wide range of dilutions. Nonetheless, the assay provided high sensitivity and showed good reproducibility with a coefficient of variation of 15% at 8

nm. Plasma samples were serially diluted with Hanks' balanced salt solution containing penicillin and streptomycin. Control or pretreatment plasma consistently had no significant effect on L1210 cell growth when the plasma was diluted 10-fold or more. Using several serial dilutions starting at 1:10 or 1:100, usually 2 plasma dilutions would give the percentage of control growth values within the log-linear range of the assay, provided that the plasma 5-aza-dCyd concentration was

30 nm. Plasma samples which showed no detectable drug at 10-fold dilution were reassayed but after 2-fold dilution and ultrafiltration through an Amicon C-25 cone. Recovery of 5-aza-dCyd after ultrafiltration was better than 90% and 6 nm 5-aza-dCyd in plasma was the limit of detection. Ultrafiltrate of pretreatment plasma or of plasma samples at 5-6 h postinfusion had no significant effect on L1210 cell growth. Possible toxicity of 5-aza-dCyd metabolites has been discounted by Covey and Zaharko (16), and in our study it is unlikely unless they are also rapidly cleared.

Visual examination of graphic plots of plasma 5-aza-dCyd concentration versus time indicated biexponential decline of drug concentration after the end of the infusion for all patients whose peak plasma drug levels were sufficiently high for adequate study. Accordingly, t1/2a and t1/2b were determined using linear regression analysis and a curve-

tripping procedure on a programmable calculator, whereby the first phase of the curve was corrected using points extrapolated from the linear regression of the second phase. The total AUC was determined by the linear trapezoidal method using the experimental points and no extrapolation. Due to the exceedingly low levels of 5-aza-dCyd after 3

following the end of infusion, extrapolation to beyond this time point could increase the AUC by <2%. The volume of distribution was calculated from the mean residence time (the area under the first moment of the plasma concentration-time curve) according to the method of Van Rossum and Van Ginneken (21) and corrected for input via an infusion as described by Lee et al. (22). Total clearance was derived by dividing the dose by the AUC:

![Graph showing the relationship between cell growth and 5-aza-dCyd concentration.](image)

Fig. 1. Standard curve for 5-aza-dCyd bioassay. L1210 cells starting at 10,000/cell were grown for 3 days in the presence of 5-aza-dCyd. Cell growth relative to control decreased exponentially with 5-aza-dCyd concentration. Drug concentration shown is that of a standard 500-nM sample which was added to 1,000 x 10^6 cell suspension. Mean values are plotted for 5 curves performed during different weeks. Bars, SE. Line drawn for 3–10 nm 5-aza-dCyd was determined by least squares analysis (r^2 = 0.98).

PHASE I STUDY OF 5-aza-dCyd

Table 1 Patient characteristics

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<th>No. of patients</th>
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<td>Men</td>
<td>15</td>
</tr>
<tr>
<td>Women</td>
<td>6</td>
</tr>
<tr>
<td>Median age (yr)</td>
<td>58 (37–75)*</td>
</tr>
<tr>
<td>Median performance status (WHO)</td>
<td>1 (0–3)*</td>
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</table>

*Numbers in parentheses, range.
RESULTS

Twenty-one patients were treated with 5-aza-dCyd with a total of 46 cycles. One patient died of progressive disease prior to completion of the first cycle and 3 patients died prior to completion of a subsequent cycle. Thus, 20 patients received 42 fully evaluable cycles. There were no drug-related deaths.

Dose-limiting toxicity consisted of reversible myelosuppression (Table 2), predominantly leukopenia. However, myelosuppression was already observed at the lower doses. Of interest, leukopenia was delayed, occurring between Days 22 and 33 after treatment. Platelet nadir was observed between Days 14 and 22. There was no dissociation between leukopenia and neutropenia at nadir. One patient developed culture-negative fever in association with a WBC of 300/mm³, requiring hospitalization and support with i.v. antibiotics. In all cases, myelosuppression was reversible. Recovery of the WBC and platelet counts was observed on Days 36-43 and Days 21-22, respectively.

Another, possibly drug-related toxicity included a mild to moderate, transient increase in serum creatinine in 3 patients. The first patient was a 69-year-old male with pulmonary and spleen metastases of a melanoma. Pretreatment serum creatinine was 1.2 mg/dl (creatinine clearance, 77 ml/min). Following therapy with 5-aza-dCyd at 30 mg/m² in 3 infusions, serum creatinine rose over 3 weeks to 1.7 mg/dl (creatinine clearance, 50 ml/min). He was treated with a second course of 5-aza-dCyd at the same dose/schedule, and a further rise in serum creatinine to 2.0 mg/dl (creatinine clearance, 45 ml/min) was observed. A renal biopsy showed a microscopic picture consistent with acute tubulointerstitial nephritis. Treatment with 5-aza-dCyd was subsequently discontinued. Further follow-up showed a gradual decrease in serum creatinine to 1.3 mg/dl at 4 months after the last treatment with 5-aza-dCyd. The second patient was a 62-year-old male with pulmonary, liver, and bone metastases of a rectal carcinoma. Pretreatment serum creatinine was 1.1 mg/dl. After 5 courses of 5-aza-dCyd at doses from 25 mg/m² in 2 infusions to 60 mg/m² in 3 infusions, no change in renal function was seen. However, following a sixth course at a dose of 75 mg/m² in 3 infusions, serum creatinine rose to 1.8 mg/dl. Follow-up of serum creatinine was not available. The patient's condition deteriorated rapidly and he died at home shortly thereafter with the diagnosis of bowel obstruction. The third patient was a 59-year-old male with local recurrence, extending to the skin of the left side of the nose and to the left eye, of an undifferentiated carcinoma of the ethmoid sinus. There was also a subdiaphragmatic 5 x 3-cm lymph node metastasis. 5-aza-dCyd was administered at a dose of 100 mg/m² in 3 infusions. Local recurrence disappeared entirely and the lymph node metastasis decreased to 1 x 1 cm. Subsequently, the subdiaphragmatic lymph node metastasis was surgically removed and was found to contain vital tumor cells on histological examination. The patient continued on 5-aza-dCyd treatment every 5–6 weeks. Fifteen months after the initiation of 5-aza-dCyd treatment there is no evidence of disease.

All other patients had short-lasting stabilization or progression of their disease.

Pharmacokinetics. Plasma concentrations of 5-aza-dCyd were examined in 15 patients during 18 courses. All but two of these courses involved the study of the first 1-h infusion. Initial examination of plasma samples from patients receiving 25–60 mg/m² indicated the need for an assay to measure submicromolar concentrations. Attempts to utilize high pressure liquid chromatography failed to achieve a sensitivity well below 0.5–1.0 µM. A bioassay similar to that described by Chabot et al. (23) gave superior sensitivity. Nonetheless, measurement of 5-aza-dCyd in patient plasma was largely restricted to doses of 75 and 100 mg/m². Fig. 2 depicts the pharmacokinetic curves for these latter doses in six patients and for 30 and 60 mg/m² in two other patients. Drug concentration increased rapidly during infusion reaching maximum levels by at least 30 min. For the highest dose studied, 100 mg/m², maximal plasma drug levels were in the micromolar range and did not exceed 4 µM. At this dose, 6 courses in 5 patients were studied. The time extremely well. Six patients (all pretreated with chemotherapy) reported mild, short-lasting nausea and vomiting at different dose levels, including the lower ones. Three patients reported mild and transient fatigue on the day of treatment. No other toxicities were observed.

Antitumor Activity. A partial response was seen in one patient, a 56-year-old male with local recurrence, extending to the skin of the left side of the nose and to the left eye, of an undifferentiated carcinoma of the ethmoid sinus. There was also a subdiaphragmatic 5 x 3-cm lymph node metastasis. 5-aza-dCyd was administered at a dose of 100 mg/m² in 3 infusions. Local recurrence disappeared entirely and the lymph node metastasis decreased to 1 x 1 cm. Subsequently, the subdiaphragmatic lymph node metastasis was surgically removed and was found to contain vital tumor cells on histological examination. The patient continued on 5-aza-dCyd treatment every 5–6 weeks. Fifteen months after the initiation of 5-aza-dCyd treatment there is no evidence of disease.

All other patients had short-lasting stabilization or progression of their disease.

Table 2 Hematotoxicity of 5-aza-dCyd

<table>
<thead>
<tr>
<th>Dose (mg/m² in 3 infusions)</th>
<th>Median nadir (× 10³/mm³)</th>
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<tbody>
<tr>
<td></td>
<td>WBC</td>
</tr>
<tr>
<td>25</td>
<td>5.6 (5.5–5.8)</td>
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<tr>
<td>25</td>
<td>4.9 (4.8–5.5)</td>
</tr>
<tr>
<td>30</td>
<td>3.7 (2.2–5.1)</td>
</tr>
<tr>
<td>40</td>
<td>3.7 (0.7–5.4)</td>
</tr>
<tr>
<td>60</td>
<td>2.8 (2.6–3.4)</td>
</tr>
<tr>
<td>75</td>
<td>2.0 (0.8–5.5)</td>
</tr>
<tr>
<td>100</td>
<td>0.9 (0.3–3.4)</td>
</tr>
</tbody>
</table>

a The first 2 patients received two 1-h infusions.
b Numbers in parentheses, range.

Fig. 2. Time course of plasma drug concentrations after start of 1-h 5-aza-dCyd infusion. Data are plotted semilogarithmically. Pharmacokinetic curves are for eight different patients represented by different symbols. ©, ▼, ▼, ▼, ▼, 100 mg/m²; △, △, △, 75 mg/m². + and × are used for two patients who received 30- and 60-mg/m² doses of 5-aza-dCyd, respectively. For courses represented by △, +, and ×, no plasma drug concentrations during infusion are given.

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course for plasma 5-aza-dCyd was similar in each case. Plasma 5-aza-dCyd disappearance was biphasic; a rapid initial phase accounted for a marked decline in 5-aza-dCyd concentration to <0.1 μM during the first h postinfusion. At 3 h after the end of the infusion, plasma 5-aza-dCyd was no longer detectable, at 6 nm. For the 75-mg/m² dose, the data for the two patients differed markedly. In one patient, 5-aza-dCyd levels followed a time course similar to that for the higher dose, while in the other patient a more rapid initial disappearance phase resulted in a plasma drug level <0.01 μM 1 h postinfusion. In two cases, at lower doses, where plasma drug levels could be determined, plasma 5-aza-dCyd disappeared monophasically below the level of detection 1 h postinfusion. Fig. 3 shows a linear plot of peak plasma drug levels for the various doses examined. In 7 of 9 patients who received doses of 25–60 mg/m², 5-aza-dCyd was below the level of detection in plasma samples taken during or at the end of the infusion. These plasma concentrations were measurable albeit rather variable, in all cases at doses of 75 and 100 mg/m². The data are insufficient for an adequate assessment for correlation; however, a trend is apparent. A line through the mean values for the higher doses would result in an X-intercept at about 50–60 mg/m². This would be consistent with the finding of low undetectable drug levels at doses below 60 mg/m².

Pharmacokinetic parameters were determined for 5-aza-dCyd at the 100-mg/m² dose for which adequate data were available. These values are given in Table 3. Mean half-lives for \( t_{1/2} \) and \( t_{1/2} \) were 7 and 35 min, respectively; similar values were obtained for lower doses. The mean peak plasma drug concentration of 2.01 μM was twice the mean value for 3 patients given 75 mg/m². The mean AUC of 408 μg-h/ml was about twice the value obtained for 75 mg/m² in the one patient for which sufficient data were available. Volume of distribution was calculated from the mean residence time which was 63 ± 6 (SE) min. The volume of distribution and clearance for the 75-mg/m² dose were similar to the mean values of 4.59 liters/kg and 126 ml/min/kg, respectively, given in Table 3. In general, the values for these parameters were considerably variable between patients. This is due to large differences between patients in plasma drug levels during infusion which account for a major portion of the AUC.

Recovery of 5-aza-dCyd in urine was examined in 11 patients for doses of 25 to 100 mg/m² (4 patients at 100 mg/m²). The percentage of administered dose found in urine ranged from <0.01 to 0.9%; there was no relationship with dose or with plasma drug levels.

DISCUSSION

This report describes the results of a clinical and pharmacokinetic study on 5-aza-dCyd. Chemical instability of 5-aza-dCyd is a major problem encountered in the clinical formulation, leading to drug solutions of decreasing potency on storage (9, 20). On the other hand, prolonged exposure to 5-aza-dCyd seems to enhance its cytotoxic properties (16). Rivard et al. (19) administered the drug as a continuous infusion in children, keeping the solution at 5-10°C and supplying fresh solutions for doses of 25 to 100 mg/m² (4 patients at 100 mg/m²). The percentage of administered dose found in urine ranged from <0.01 to 0.9%; there was no relationship with dose or with plasma drug levels.

Other nonhematological side effects were essentially absent in the present study. Mild nausea and vomiting, which were reported by some of our patients who were all heavily pre-
treated, might have been anticipatory. In contrast, more serious nausea and vomiting, in addition to liver function disturbances and a neuromuscular syndrome, have been reported as side effects of 5-azacytidine (26).

In the phase I study in childhood leukemia (19), gastrointestinal toxicity was also reported to be minimal. However, some patients in that study, receiving 2 or more courses, were reported to have developed alopecia.

We were encouraged by the partial response observed in one of our patients, suggesting a potential use of 5-aza-dCyd in the treatment of solid tumors. This possibility is also suggested by the results of recent experiments in our laboratory showing that (a) 5-aza-dCyd after a 24-h exposure has the same cytotoxicity in various solid tumor-derived cell lines when compared to the leukemia cell lines HL-60 and CEM (27) and (b) 5-aza-dCyd treatment causes tumor growth delay in human tumor xenografts of head and neck cancer transplanted in nude mice (28).

A bioassay was necessary to measure 5-aza-dCyd concentrations in plasma and urine. Due to submicromolar 5-aza-dCyd concentrations and interfering plasma substances, we were unable to utilize a high pressure liquid chromatography method with the required sensitivity, although plasma drug concentrations of 2–3 μM determined in 2 patients with the bioassay could be confirmed chromatographically (data not shown). The bioassay based on L1210 cell drug sensitivity has been utilized in a phase I study on 5-aza-dCyd in childhood leukemia (19) and for pharmacokinetics studies in animals (23, 29) measuring drug concentrations as low as 0.1 μg/ml (approximately 0.4 μM).

In animal studies high pressure liquid chromatography (16, 23) and ³H-labeled drug (16) have been used to determine high and low plasma drug concentrations, respectively. Using a more microscale culture system, we were able to use the L1210-based bioassay to reach a sensitivity level of 6 nM in plasma.

In the study of 5-aza-dCyd in pediatric leukemic patients (19), little information was reported on the pharmacokinetics of 5-aza-dCyd. A drug infusion rate of 1 mg/kg/h yielded plasma concentrations of about 0.5 μg/ml (approximately 2 μM) which decreased with a half-life of 12 min. In our study we found a more rapid initial decrease in plasma drug levels (t½ α of 7 min). With the assay of 5-aza-dCyd to a lower limit of detection, we were able to detect a second phase below plasma drug concentration of 0.1 μM (t½ β of 35 min). Covey and Zaharko (16) have provided detailed pharmacokinetic data for 5-aza-dCyd in the mouse, finding a triexponential disappearance of 5-aza-dCyd from plasma with half-lives of 11, 32, and 365 min. The pharmacokinetics of 5-aza-dCyd appear to be similar in humans and mice, except for the protracted final half-life seen in mice but not in our study. Unlike in our study, mice were shown to have long-lasting plasma drug levels of 0.01 to 0.1 μg/ml (approximately 0.04 to 0.4 μM) 4–8 h following administration of 5-aza-dCyd (10 or 100 mg/kg).

The clearance of 5-aza-dCyd in patients at the doses studied was higher than that reported for mice (16) and rabbits and dogs (23). Since renal clearance in the present study was apparently negligible, it is likely that metabolism of 5-aza-dCyd was the major clearance process. In the mouse, renal clearance is a substantial portion of the total clearance at a 100-mg/kg dose of 5-aza-dCyd, but its role is markedly decreased with lower doses (16).

Nonmetabolic degradation due to ring opening has been noted by Covey and Zaharko (16) to result in a drug half-life of 17.5 h at 37°C. It is therefore unlikely that drug instability could account for the rapid plasma disappearance of 5-aza-dCyd. It is possible that in humans 5-aza-dCyd is rapidly eliminated largely by deamination. In rabbits and drugs (23), two species which have relatively low tissue cytidine deaminase levels (30), t½ ⁴ but not t½ ⁶ of 5-aza-dCyd was longer than in humans and mice. Therefore the second plasma drug disappearance phase does appear to involve the deamination process.

The data for 100 mg/m² indicate that 5-aza-dCyd clearance proceeds at a rate much in excess of the liver blood flow (about 1400 ml/min). Thus, extrahepatic metabolism of 5-aza-dCyd accounts for much of the drug clearance. It was not possible to calculate the clearance for most of the lower dose courses examined. However, a rough approximation could be made when comparing peak plasma drug levels for 100 mg/m² (2 μM) to those for 25–60 mg/m² (<0.01 μM). The total clearance for the lower doses could be in the order of 100 times higher than for the 100-mg/m² dose. This marked difference suggests a saturation of some elimination process(es) at doses greater than 60 mg/m². Saturation of cytidine deaminase seems unlikely considering the relatively high Km (250 nM) for 5-aza-dCyd (31). If anabolism was the saturating elimination process at the doses studied, substantial 5-aza-dCyd incorporation into DNA could explain the bone marrow toxicity seen at the lower doses as well. These dose-dependent pharmacokinetics data may explain the observed toxicity with our schedule using total doses as much as 8 times lower compared with those used in continuous infusions (19), thus indicating a possibly greater toxicity with the present schedule. However, it cannot be ruled out that intermittent administration of 5-aza-dCyd can be as effective as continuous infusions in providing prolonged drug exposure.

Finally, on the basis of the observed myelosuppression it is recommended that using the schedule of the present study in phase II studies in solid tumors, 5-aza-dCyd should be administered at a dose of 75 mg/m² in 3 infusions every 5 weeks. In cases where myelosuppression is mild one may consider escalating the dose to the maximum tolerated dose of our study.

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REFERENCES

**Phase I and Pharmacokinetic Study of 5-Aza-2′-deoxycytidine (NSC 127716) in Cancer Patients**


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