

# Pharmacokinetics of Continuous Infusion of Methotrexate and Teniposide in Pediatric Cancer Patients<sup>1</sup>

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## ABSTRACT

Laboratory studies have demonstrated the ability of teniposide to markedly enhance the intracellular accumulation of methotrexate suggesting that combination therapy with these agents may produce clinical benefit. Studies of methotrexate and teniposide were conducted in 19 children with relapsed acute lymphocytic leukemia to evaluate the pharmacokinetics of this previously untested combination of agents given alone or in combination and to demonstrate the feasibility of a Bayesian dose optimization strategy. Patients were randomly assigned to receive intermediate dose methotrexate as a 24-h continuous infusion, administered either simultaneously with continuous infusion teniposide or sequentially with the teniposide infusion beginning 12 h after the end of the methotrexate infusion. Plasma samples were obtained during and after infusions at appropriate times for a comprehensive pharmacokinetic study of each drug. Two measured drug concentrations obtained during the infusion were used to adjust each patient's dose rate to achieve target values of 10  $\mu\text{M}$  for methotrexate and 15  $\mu\text{M}$  for teniposide. Pharmacokinetic parameters for teniposide were not different for patients given simultaneous methotrexate from parameters estimated for patients receiving teniposide 12 h after the end of the methotrexate infusion. Despite similar end of infusion methotrexate concentrations, 24-h postinfusion methotrexate concentrations were lower (0.137 versus 0.235  $\mu\text{M}$ ;  $P < 0.05$ ) in the patients receiving simultaneous infusions. The patient specific dose regimens yielded acceptably precise, minimally biased steady state drug concentrations. These pharmacokinetic results provide the basis for further clinical studies with this combination of antileukemic agents.

## INTRODUCTION

The use of combinations of anticancer agents with complementary mechanisms of cytotoxicity is intuitively appealing and of demonstrated theoretical (1, 2) and clinical (3, 4) benefit. *In vitro* studies have shown enhanced intracellular accumulation of methotrexate and methotrexate polyglutamates in the presence of teniposide at concentrations (5) that are achievable in patients. This cellular interaction and the well established independent antileukemic activity of both methotrexate (6) and teniposide (7-9) provide a compelling rationale for evaluating this previously untested combination of drugs in pediatric cancer patients.

A continuous infusion regimen, at doses of each drug known to be independently effective and well tolerated (6, 10), was selected to evaluate clinically the *in vitro* cellular interaction between teniposide and methotrexate. However, when fixed doses of these drugs are administered, interpatient variability in systemic clearance has been shown to yield steady state serum concentrations that vary over at least a 4-5-fold range (6, 10, 11). More importantly, it has been demonstrated that variability in methotrexate and teniposide pharmacokinetics influences

patient outcome (6, 10). To control for interpatient pharmacokinetic variability as a confounding factor in the evaluation of these agents, we developed a pharmacokinetic strategy for design of patient specific dosage regimens that would permit us to achieve target plasma concentrations. The specific study objectives were to determine the pharmacokinetics of methotrexate and teniposide given alone or simultaneously and to evaluate the reliability of a clinically feasible dose optimization strategy for these two important anticancer agents.

## MATERIALS AND METHODS

**Patient Eligibility and Clinical Protocol.** Patients younger than 21 years at diagnosis with acute lymphocytic leukemia in their first or second bone marrow relapse ( $>25\%$  lymphoblast) were eligible for this study. Patients were excluded for impaired renal (serum creatinine  $>1.2$  mg/dl) or hepatic (bilirubin  $>2.0$  mg/dl, serum glutamic-oxaloacetic transaminase 3 times normal value) function not attributable to the recurrent leukemia. Informed consent was obtained according to institutional guidelines.

The pharmacokinetic studies of methotrexate and teniposide were conducted prior to beginning a 4 drug reinduction regimen comprised of prednisone, vincristine, daunomycin, and L-asparaginase. In addition to the systemic pharmacokinetic studies reported here, bone marrow aspirates were obtained from a subset of patients to examine intracellular pharmacokinetics of the polyglutamylation of methotrexate in the presence and absence of teniposide. The results of this study have been published elsewhere (12).

**Drug Administration and Blood Sampling.** Patients were randomized to receive methotrexate simultaneously with teniposide or sequentially with teniposide beginning 12 h after the end of the methotrexate infusion (Fig. 1). A 12-h interval following the end of the methotrexate infusion assured that methotrexate plasma concentrations would fall below 1  $\mu\text{M}$  before beginning the teniposide infusion. This minimized the possibility of sequentially administered teniposide influencing the systemic or cellular pharmacokinetics of methotrexate for comparison to the group receiving simultaneous methotrexate and teniposide. Methotrexate was administered as a loading dose of 200 mg/m<sup>2</sup> i.v. over 30 min followed by a 24-h infusion at an initial rate of 34.6 mg/m<sup>2</sup>. Leucovorin rescue was started 12 h after the end of the methotrexate infusion. The loading dose of teniposide was 45 mg/m<sup>2</sup> over 1 h followed by an initial maintenance rate of 8.3 mg/m<sup>2</sup>/h for 36 h ( $n = 14$ ) or 72 h ( $n = 5$ ).

Unexpected serious gastrointestinal and hematological toxicity observed in the initial five patients treated with either sequential or simultaneous methotrexate and 72-h teniposide infusions required a protocol amendment to reduce the teniposide infusion time to 36 h (4). Our previous studies with teniposide as short infusions (3) or continuous infusions for 72 h as a single agent at doses up to 750 mg/m<sup>2</sup> (10) had demonstrated only mild or moderate gastrointestinal toxicity.

Teniposide (10 mg/ml ampuls supplied by the National Cancer Institute) was diluted in 5% dextrose to a final concentration of 0.2 mg/ml. Methotrexate (Lederle; 100 mg/ml) was diluted in 5% dextrose to a final concentration of 4 mg/ml. Stability was demonstrated for up to 24 h for each drug alone and for 4 h when combined at the final dilutions.<sup>3</sup> Both drugs were administered with a volumetric infusion device (IVAC 560).

<sup>3</sup> Unpublished data.

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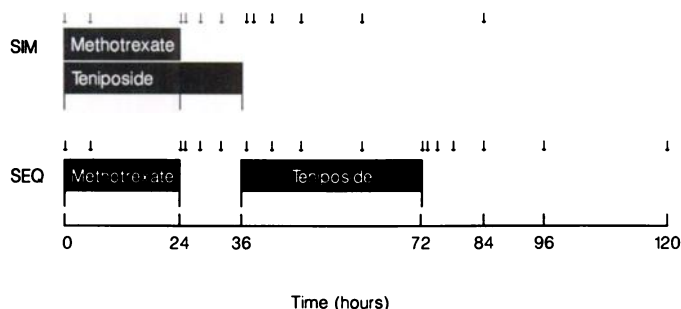


Fig. 1. Drug administration schedules and blood sampling strategies for the simultaneous (SIM) and sequential (SEQ) treatment arms. Arrows, times at which blood samples were obtained for methotrexate and/or teniposide concentrations. In 5 patients the teniposide infusions were 72 h in duration rather than 36 h.

Four blood samples were obtained for methotrexate analysis during the infusion and 8 samples were obtained up to 60 h after the infusion. For teniposide, 5 blood samples were obtained during the infusion and 6 samples were obtained at intervals up to 48 h postinfusion. The scheme for pharmacokinetic study design is shown in Fig. 1. Blood samples (3–4 ml) were collected into heparinized tubes and the plasma was analyzed immediately (1- and 6-h samples) or frozen at  $-70^{\circ}\text{C}$  until the time of analysis. The dosage regimens for methotrexate and teniposide were adjusted within 12 h from the start of the infusions using measured drug plasma concentrations obtained at 1 and 6 h to achieve target steady state concentrations of  $10\ \mu\text{M}$  for methotrexate and  $15\ \mu\text{M}$  for teniposide.

**Drug Assay and Pharmacokinetic Analysis.** Plasma samples were assayed for methotrexate by fluorescence polarization immunoassay (Tdx; Abbott Laboratories, Diagnostic Division, Irving, TX). The lower limit of quantification of this assay was  $0.05\ \mu\text{M}$  with between day coefficients of variation of 9.2% at  $0.07\ \mu\text{M}$  and 4.2% at  $50.00\ \mu\text{M}$ . A sensitive and specific high performance liquid chromatography method using electrochemical detection, developed in our laboratory, was used to determine plasma concentrations of teniposide (13). The sensitivity of this assay was  $0.38\ \mu\text{M}$  with interday coefficients of variation of 5.3% at  $0.46\ \mu\text{M}$  and 8.2% at  $27.4\ \mu\text{M}$ .

A Bayesian estimation algorithm (14) was used to determine patient specific pharmacokinetic parameters for a two compartment model based on measured drug concentrations obtained at the end of the loading infusion and at least 5 h after the beginning of the maintenance infusion rate. The population priors for the two compartment models for methotrexate (10) and teniposide (6) were derived from previously published studies at our institution. The variance for the observations was assumed to be proportional to the measured values with a coefficient of variation of 10%. Revised dose rates were calculated to achieve the target steady state concentrations for methotrexate ( $10\ \mu\text{M}$ ) and teniposide ( $15\ \mu\text{M}$ ) and were adjusted if the revised dose rates differed from the scheduled dose rate by more than 10%.

Maximum *a posteriori* Bayesian estimation, as implemented for this study, assumes the model parameters are uncorrelated and normally distributed. Under these assumptions, application of maximum likelihood estimation to Bayes theorem yields the following objective function:

$$\text{OBJ}_{\text{MAP}} = \sum_{i=1}^m \frac{(\hat{C}_i - C_i)^2}{\sigma_i^2} + \sum_{j=1}^n \frac{(\hat{P}_j - P_j)^2}{\sigma_j^2}$$

where  $P_j \dots P_n$  are the prior estimates of the population means for the model parameters and  $\hat{P}_j \dots \hat{P}_n$  are the parameter estimates for a subject given  $C_i$ , the measured concentrations, and the variances for the observation(s)  $\sigma_i^2$  and the parameters  $\sigma_j^2$ . The revised objective function then yields a posterior estimate of the individual subject's average parameters even in the instance where data are limited and study design is suboptimal. This approach has been shown to be reliable for other drugs such as phenytoin and lidocaine even when sampling times do not extend over several half-lives (14).

After the completion of the study, a two compartment model was fit to the complete data sets for methotrexate ( $n = 12$ ) and teniposide

( $n = 11$ ) using weighted nonlinear least squares with the ADAPT modeling software (15). The parameters estimated were the volume of the central compartment ( $V_c$ ), distribution rate constants ( $K_{cp}$  and  $K_{pc}$ ), and the elimination rate constant ( $k_{el}$ ). The parameters clearance ( $Cl$ ), terminal half-life ( $t_{1/2\beta}$ ), volume of distribution at steady state ( $Vd_{ss}$ ) were calculated. Dosage regimen optimization was done using the USC\*Pack software provided by the Laboratory of Applied Pharmacokinetics, University of Southern California, and modified by our laboratory for teniposide and methotrexate. The Wilcoxon rank sum test was used to test for significance between treatment groups. Comparative and descriptive statistics were done with the SAS statistical package.

## RESULTS

Twenty-two consecutive patients with relapsed acute lymphocytic leukemia were eligible for enrollment. Two patients refused consent for the pharmacokinetic studies and 1 patient was excluded because of impaired liver function. Patient demographics for the 19 evaluable subjects are summarized in Table 1. There were no significant differences between the 2 groups with respect to age, body surface area, weight, or height. Nine patients were randomized to the simultaneous methotrexate and teniposide infusions and 10 patients received sequential therapy.

**Dose Regimen Optimization.** For teniposide, a decrease in dose rate of 13% to 38% was required in 4 patients and an increase of 42% to 67% in 4 patients. Dose adjustments and achieved end of infusion concentrations (Table 2) were similar in the simultaneous and sequential groups. The median model predicted concentration at the end of the infusion was  $14.52\ \mu\text{M}$  (range,  $8.28$ – $32.57\ \mu\text{M}$ ) for patients in whom a dose adjustment was made ( $n = 8$ ) and  $17.94\ \mu\text{M}$  (range,  $7.95$ – $26.42\ \mu\text{M}$ ) for patients ( $n = 11$ ) not requiring dose adjustments. The coefficient of variation for the end of infusion concentrations in all patients was 35%.

To achieve the methotrexate target concentrations, dose adjustments were required for 8 of the 9 patients in the simultaneous group and 7 of the 10 patients in the sequential group. The dose adjustments ranged from 11 to 56% of the initial dose rate; the final dose rate was reduced in 14 of 15 subjects. In the group of patients requiring dose adjustments, the median (range) end of infusion concentration was  $9.36$  ( $7.10$ – $14.9$ )  $\mu\text{M}$ . Patients not requiring a dose adjustment had a median concentration of  $9.25$  ( $8.12$ – $12.2$ )  $\mu\text{M}$ . The median (range) for adjusted dose rates and end of infusion concentrations are shown for all 19 patients in Table 3. The coefficient of variation for the end of the infusion methotrexate concentrations in all subjects was 17% while the coefficient of variation was 31% for the clearance estimates.

The median measured methotrexate ( $9.7\ \mu\text{M}$ ) and teniposide ( $16.9\ \mu\text{M}$ ) concentrations (●) are shown (Fig. 2) before and after

Table 1 Patient characteristics

Patient characteristics were similar in the two groups of patients. Values shown are means except for gender (F = female) and relapse which indicate actual number.

Feature	SIM* (n = 9)	SEQ (n = 10)
Age (yr)	7.9	7.5
BSA ( $\text{m}^2$ )	1.1	1.1
Wt (kg)	30.9	35.4
Ht (cm)	130	125
Gender	2F	2F
First relapse <sup>b</sup> (no. of patients)	8	7

\* SIM, simultaneous methotrexate and teniposide; SEQ, sequential methotrexate and teniposide; BSA, body surface area.

<sup>b</sup> Remaining patients were in second hematological relapse.

Table 2 Teniposide pharmacokinetic parameters

The median (range) values for teniposide pharmacokinetic parameters were similar between the groups receiving simultaneous (SIM) and sequential (SEQ) infusions. Estimates for clearance ( $Cl$ ) and terminal half-life ( $t_{1/2\beta}$ ) were similar to previous studies in similar patients (10). The steady state concentrations are mean (range) model predicted values from the complete pharmacokinetic study of each subject.

	SIM (n = 9)	SEQ (n = 10)	Entire group (n = 19)
$Cl$ (ml/min/m <sup>2</sup> )	13.43 (8.34–24.13)	12.70 (5.11–28.62)	13.43 (5.11–28.62)
$t_{1/2\beta}$ (h)	9.56 (4.96–13.04)	8.18 (3.76–24.54)	9.48 (3.76–24.54)
Steady state concentration	15.6 (8.3–23.8)	17.7 (8.0–23.2)	16.1 (8.0–23.8)
Final dose rate (mg/h/m <sup>2</sup> )	8.6 (6.2–14.0)	8.5 (5.3–13.6)	8.6 (5.3–14.0)

Table 3 Methotrexate pharmacokinetic parameters

The median (range) values for methotrexate pharmacokinetic parameters were similar between groups although clearance ( $Cl$ ) was suggestively lower ( $P = 0.09$ ) for the simultaneous (SIM) group. The steady state concentrations are the mean (range) model predicted values from the complete pharmacokinetic study of each subject. The 48-h concentration is the measured value 24 h following the end of the 24-h infusion and is significantly lower in the SIM group. SEQ, sequential infusion.

Parameter	SIM (n = 9)	SEQ (n = 10)	Entire group (n = 19)
$Cl$ (ml/min/m <sup>2</sup> )	89.50 (67.02–104.36)	106.10 (42.25–167.13)	96.73 (42.25–167.13)
$t_{1/2\beta}$ (h)	6.80 (4.82–24.39)	8.43 (5.21–20.57)	7.29 (5.21–24.39)
Steady state concentration	9.66 (7.1–10.9)	9.72 (7.4–14.9)	9.72 (7.1–14.9)
48 h concentration ( $\mu$ M)	0.137 (0.075–0.190)	0.235 (0.090–0.280)	0.152 (0.075–0.280)
Final dose rate (mg/h/m <sup>2</sup> )	24.2 (17.1–29.4)	27.75 (15.9–40.7)	25.8 (15.9–40.7)

12 h of therapy when dosage regimen adjustments were made. The error bars represent 1 SD and the solid line a simulation of median pharmacokinetic parameters from the complete pharmacokinetic data analysis.

**Complete Pharmacokinetic Analysis.** All pharmacokinetic parameter estimates for teniposide were similar in the simultaneous and sequential groups (Table 2). The median values (ranges) for teniposide parameter estimates for all 19 patients were:  $V_c$  2.17 (1.20–4.95) liters/m<sup>2</sup>,  $K_{el}$  0.36 (0.16–0.53) h<sup>-1</sup>,  $K_{cp}$  0.18 (0.01–0.91) h<sup>-1</sup>, 0.20 (0.04–0.48) h<sup>-1</sup>. The median  $Cl$ ,  $t_{1/2\beta}$ , and  $Vd_{ss}$  for all patients were 13.43 ml/min/m<sup>2</sup>, 9.48 h, and 4.85 liters/m<sup>2</sup>, respectively. Final teniposide dose rates were similar in both groups.

The median values (ranges) for the methotrexate pharmacokinetic parameters based on all measured drug concentrations were  $V_c$  10.30 (2.44–19.78) liters/m<sup>2</sup>,  $K_{el}$  0.54 (0.04–0.80) h<sup>-1</sup>,  $K_{cp}$  0.07 (0.02–0.33) h<sup>-1</sup>, and 0.11 (0.03–0.20) h<sup>-1</sup> and did not differ between the 2 groups. However, the patients receiving simultaneous methotrexate and teniposide had significantly lower 48-h (*i.e.*, 24-h postinfusion) methotrexate concentrations (Fig. 3) despite median systemic methotrexate clearances (Table 3) that tended to be lower ( $P < 0.09$ ) than those found in patients given methotrexate alone. The methotrexate terminal half-lives and median final dose rates were similar ( $P = 0.24$  and 0.49, respectively) in the simultaneous and sequential groups. This finding is consistent with *in vitro* studies demonstrating enhanced intracellular retention of methotrexate in the presence of teniposide (10).

## DISCUSSION

Combined use of methotrexate and teniposide warrants clinical evaluation based on *in vitro* studies suggesting that teniposide can enhance formation of intracellular polyglutamates of methotrexate, yielding increased cytotoxicity (5, 12). The results of the pharmacokinetic studies reported here demonstrate that these two drugs can be given together without any changes in the disposition of teniposide. The differences observed in methotrexate disposition are modest and indicate that this combination can be used without any alteration in dose.

Previous studies from our laboratory have demonstrated substantial interpatient pharmacokinetic variability for methotrexate (6) and teniposide (10) and, more importantly, have identified a relationship between pharmacokinetic parameters and the clinical outcome of therapy (6, 10). Patients with higher clearance and lower steady state concentrations of methotrexate are at increased risk for early relapse, while patients with lower clearances and higher steady state concentrations of either drug are at increased risk for toxicity.

As in previous investigations, we found clearances that ranged

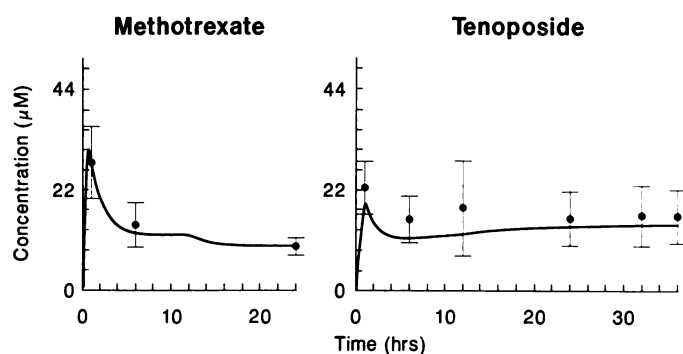


Fig. 2. ●, bars, measured concentrations at 1 h and 6 h before dosage adjustment and following dosage adjustment at 24 h (for methotrexate and 12, 24, and 36 h for teniposide). —, computer simulation based on median parameters from the complete pharmacokinetic analysis and mean doses actually given for each drug.

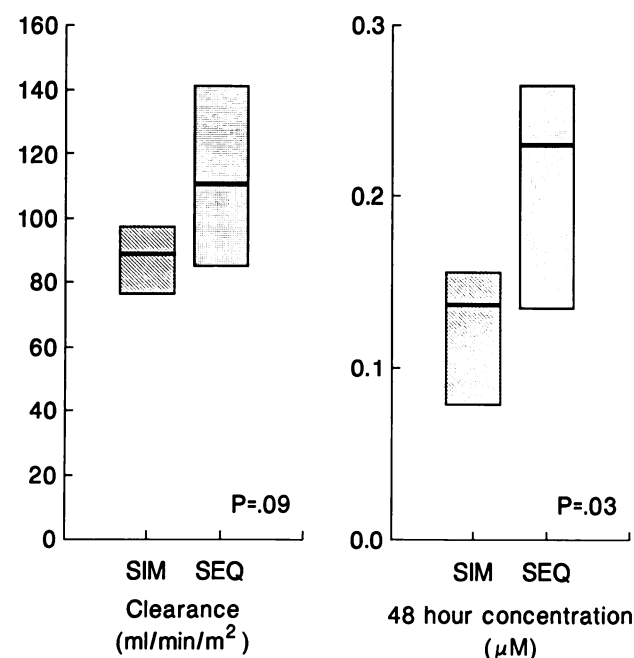


Fig. 3. Methotrexate clearances and 48-h concentrations (24 h postinfusion) for the simultaneous (SIM) and sequential (SEQ) treatment arms. Data are presented as medians (bars) and interquartile ranges.

over a 4–5-fold range for both drugs in this study. With only 2 measured drug concentrations, we now show in a prospective study that target concentration of teniposide and methotrexate can be achieved with a reasonable degree of precision (Fig. 2). Despite extensive interpatient pharmacokinetic variability, the coefficient of variation for methotrexate concentrations was less than 20% after dosage adjustment and was approximately 35% for teniposide. The somewhat greater variability for teniposide is largely due to the difficulty of reliably estimating clearance from data obtained during the initial 6 h of therapy for a drug with an average half-life of 10 h.

The variability in plasma concentration profiles due to interpatient differences in pharmacokinetics is illustrated for teniposide in Fig. 4. The 5-fold range of simulated concentrations shown is a consequence of an equivalent degree of interpatient variability in drug clearance. The ability to estimate patient specific pharmacokinetic parameters with as few as two measured drug concentrations allows dose adjustments to control this variability and the associated concentration related effects. The feasibility and clinical utility of patient specific dosage regimens for aminoglycosides (16), anticonvulsants (17, 18) and antiarrhythmic drugs (19, 20) are well recognized but only limited experience with anticancer drugs have been published to date (21, 22).

The vast majority of previously published experience with pharmacokinetic strategies for dosage regimen optimization has been limited to one compartment models (16) or simple proportional dose adjustments requiring the assumption of steady state (21). The use of Bayesian estimation for more complex pharmacokinetic models with small numbers of measured drug concentrations has been suggested by others (22, 23) but has not been prospectively evaluated in pediatric cancer patients. These results with methotrexate and teniposide demonstrate the ability to control for interpatient pharmacokinetic variability of anticancer drugs and thus increase the likelihood of a positive therapeutic outcome. It is apparent from the higher coefficient of variation for the predicted teniposide concentrations that a longer sampling interval would improve the precision of dose adjustment.

The methotrexate plasma concentrations at 24 h postinfusion were significantly lower in the patients receiving simultaneous teniposide, despite similar administered doses, clearance, and end of infusion plasma concentrations of methotrexate (Fig. 2). This finding may be attributable to inhibition of efflux by teniposide and conversion to higher chain polyglutamate forms

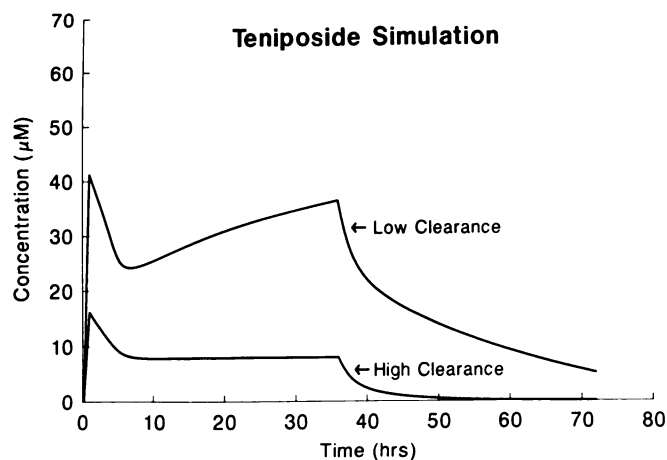


Fig. 4. Simulated teniposide concentration profiles for a patient with a low clearance and a patient with a high clearance for a fixed dose of 45 mg/m<sup>2</sup> as a 1-h loading infusion followed by 200 mg/m<sup>2</sup>/24 h.

that are retained intracellularly. Alternatively, lower methotrexate plasma concentrations 24 h postinfusion in the simultaneous group could be explained by higher systemic methotrexate clearances in these patients. However, the median clearances (Table 3) were actually lower for the simultaneous group although not statistically significantly different ( $P = 0.09$ ).

The methotrexate concentration 24 h postinfusion is largely determined by tissue distribution rather than systemic clearance. Thus the finding of lower values in the simultaneous group is consistent with prolonged intracellular retention of methotrexate as would be predicted from the *in vitro* work. Studies from bone marrow blast cells in a subset of these patients did demonstrate a 2-fold increase in exchangeable intracellular antifolate (12) but due to substantial interpatient variability in conversion of methotrexate to higher polyglutamylated forms no increase in total intracellular folate could be demonstrated. More definitive cellular studies are needed to conclusively support this hypothesis.

The gastrointestinal and hematological toxicities that occurred in the initial 5 patients given 72-h teniposide infusions suggest an additive effect with methotrexate, inasmuch as these agents are well tolerated when given alone at the dosages used in this study (6, 10). This clinical observation in conjunction with the possibility of enhanced cellular retention of methotrexate support an interaction between these two drugs; it remains to be determined whether enhanced effects on tumor cells can be achieved without undue host toxicity.

In summary, the feasibility of combined therapy with methotrexate and teniposide has been shown. The pharmacokinetic studies provide a basis for designing rational initial dosage regimens for these drugs given in combination and demonstrate the reliability of a dosage regimen optimization strategy requiring only two measured drug concentrations to determine patient specific pharmacokinetic parameters. While patient response was not an objective for this study, we did observe decreased marrow cellularity after methotrexate and teniposide and 2 patients had marrow aspirates with no leukemic blasts and evidence of active hematopoiesis. Further studies appear warranted with this previously untested combination of antileukemic drugs.

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