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Clinical pharmacodynamics of continuous-infusion etoposide

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Summary. Continuous-infusion etoposide was given to 15 patients with newly diagnosed small-cell lung cancer (extensive disease) and 10 patients with various refractory malignancies. The untreated patients with lung cancer received 200 mg/m^2 etoposide over 24 h in combination with 100 mg/m^2 cisplatin, and the pretreated patients received 400 mg/m^2 etoposide over 36 h as monotherapy. Pharmacokinetic studies of etoposide were carried out in all patients. High-performance liquid chromatography (HPLC) was used to measure etoposide. All patients had normal hepatic and renal function tests and were followed weekly for hematologic toxicity after therapy. In all, 14 untreated and 9 pretreated patients were evaluable. Biostatistical analysis was done to correlate pharmacokinetic results to hematologic effects. Pearson correlation coefficients were calculated for continuous variables (i. e., blood counts), and Spearman correlation coefficients were calculated for ranked variables (i. e., toxicity grades). The values for the area under the plasma concentration vs time curve (AUC) and systemic clearance varied widely among patients. However, the AUC and clearance were significantly correlated ($P < 0.05$) with the WBC and platelet nadirs and the decrease in hemoglobin. The grade of leukopenia and total grade of hematologic toxicity were also correlated with AUC and clearance. Because the interpatient variability in etoposide pharmacokinetics correlates with the variable degree of hematologic toxicity, pharmacokinetic drug monitoring is suggested.

Introduction

Etoposide is an antineoplastic agent with proven clinical efficacy in a variety of malignancies [5]. Although its mechanism of action is not completely understood, it may stabilize type II topoisomerase-DNA complexes, preventing rejoining of single- and double-strand breaks. It delays cell transit through the S phase and produces cell-cycle arrest in the late S or early G_2 phase [4, 5]. In a clonogenic assay against human tumor-cell lines, a significant correlation between duration of drug exposure and cytotoxicity was demonstrated [13]. Greater antitumor activity was found when etoposide was given in repeated rather than single doses in mice bearing leukemia [3].

Because these data indicated that extending the duration of exposure correlated with improved efficacy, Bennett et al. [1] have carried out a clinical and pharmacological study of continuous-infusion etoposide in patients with advanced malignancies. Their study showed that both the plasma drug concentration at steady state and the plasma concentration at 24 h from the start of infusion correlated with hematologic toxicity, especially leukopenia. Based on these data, Ratain et al. [7] proposed an adaptive control regimen for etoposide with dose adjustment during continuous infusion. Although these authors could not demonstrate an advantage to their adaptive control scheme (because of apparent bias of their model from a previous study), they concluded that this approach is feasible if the large interpatient pharmacokinetic and pharmacodynamic variability is taken into account. Rodman et al. [8] have used a related drug, teniposide, in continuous infusions in children with recurrent leukemia, lymphoma, and neuroblastoma. Interpatient pharmacokinetic variability in their study yielded a 4- to 6-fold difference in intensity of systemic exposure within the same dose level, which was an important determinant of clinical response.

Given the narrow therapeutic index of antineoplastic agents, it appears desirable to individualize dosing on the basis of measurable pharmacokinetic parameters. From the above studies, it has only recently become evident that etoposide exhibits significant relationships between the extent of myelosuppression and pharmacokinetic parameters. In the present study, we sought to investigate this relationship in both untreated and pretreated patients. A group of newly diagnosed patients with small-cell lung cancer (extensive disease) was given etoposide by continuous infusion, with concomitant infusion of cisplatin. Another group of patients with a variety of refractory malignancies received single-agent etoposide in a continuous infusion.

Materials and methods

A total of 15 untreated patients with newly diagnosed small-cell lung cancer (extensive disease) were entered on study after informed consent was obtained. A dose of 200 mg/m^2 etoposide was given in a continuous infusion over 24 h; 100 mg/m^2 cisplatin was given concomitantly over 24 h in a separate infusion bag. Serial plasma samples

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were obtained during infusion (4 samples) and up to 48 h after infusion (10–13 samples). Samples were drawn from an extremity opposite the infusion site. Of the 15 patients, 1 was inevaluable because of inadequate sampling. All 14 evaluable patients were male Caucasians with a median age of 60 years (range, 46–75 years). The median ECOG (Eastern Cooperative Oncology Group) performance status in this group was 1 (range, 1–2).

Ten patients were entered on a protocol of 400 mg/m^2 etoposide given as a continuous infusion over 36 h. In this group, two patients had small-cell lung cancer, two had been diagnosed as having non-small-cell lung cancer, two had testicular cancer, and one each had acute myelomonocytic leukemia, acute lymphocytic leukemia, osteogenic sarcoma, and malignant fibrous histiosarcoma. Nine patients were evaluable and one did not return for follow-up. The median age in this group was 42 years (range, 18–69 years), and the median ECOG performance score was 2 (range, 1–3). All patients in this group had been pretreated with chemotherapy (median number of courses), 6; (range, 4–12); all except one were men. Serial plasma samples were obtained during (4 samples) and up to 72 h after (15–18 samples) infusion.

All 25 patients had normal hepatic (bilirubin, transaminases) and renal [blood urea nitrogen (BUN), creatinine] function. Patients were followed weekly in clinic for white blood cell count, hemoglobin/hematocrit, and platelet count. Hematologic toxicity was graded according to the Common Toxicity Criteria of the National Cancer Institute (USA). In addition to nadir counts, absolute decreases (pre- minus posttreatment values) and relative decreases (absolute decrease divided by pretreatment values) in hematologic values were calculated.

Plasma samples were analyzed for etoposide by isocratic high-performance liquid chromatography (HPLC), with teniposide (VM26) as the internal standard. Water and solvents used in analysis were of HPLC grade. Pure standards of etoposide and teniposide were kindly provided by Bristol Laboratories (Evansville, Ind). A 1-ml sample of plasma was added onto disposable silica C18 columns (1 cm^3; J.T. Baker Inc., Phillipsburg, NJ), washed with 1 ml isopropylether, and extracted with 2 × 1 ml 2:1 (v:v) chloroform:acetonitrile. The eluant was dried under nitrogen and reconstituted with 0.1 ml 60:40 (v:v) water:acetonitrile, and 20 µl was injected on the HPLC column. The mobile phase consisted of 62:37:1 (by vol.) water:acetonitrile:glacial acetic acid that was filtered before use and sparged with helium. A micro-Bondapak phenyl column (dimensions, 3.9 × 300 mm; particle size, 10 µm) was used. The column and the following equipment were from Waters Chromatography (Milford, Mass): WISP cooled automatic injector, M510 pump, M441 UV detector at 254 nm, and M840 software on a DEC350 computer.

At a flow rate of 1.5 ml/min, the retention times were 3.8 min for etoposide and 9.1 min for teniposide. Etoposide extraction efficiency with the described method was 75%. The detection limit for etoposide was 0.1 µg/ml. Coefficients of variation for within- and between-day HPLC injections were <10% (same day, 4.5%, between days, 6.2%).

The area under the concentration vs time curve (AUC) was calculated using the logarithmic trapezoidal method [14]. The terminal elimination rate constant was determined by log-linear least-squares regression of the plasma concentration time points in the terminal phase of the plasma disposition curve. This value was used to extrapolate the area from the last measured concentration to infinity. Etoposide systemic clearance and volume of distribution at steady state were calculated using standard pharmacokinetic equations [6, 10]. Pearson correlation coefficients were calculated for continuous variables (i.e., blood counts), and Spearman correlation coefficients were calculated for ranked variables (i.e., toxicity grades).

Table 1. Pharmacokinetics and hematologic toxicity of etoposide (200 mg/m^2 as 24-h infusion) in untreated small-cell lung cancer

Patient number	AUC_{0-00} (mg-h/l)	Vd_{ss} (l/m^2)	Cl_p (ml/min per m^2)	Before therapy:			Nadir counts:			Toxicity[a] grade
				WBC	Hgb	Plt	WBC	Hgb	Plt	
1	242	11.9	12.7	7.6	15.3	311	0.7	11.6	44	4
2	186	11.4	18.3	5.6	8.8	440	3.4	8.4	321	2
3	187	10.8	17.3	6.8	13.3	455	2.6	10.7	290	2
4	147	10.0	23.5	3.3	11.8	175	2.2	11.7	187	2
5	111	11.5	29.7	13.3	9.8	506	4.5	10.3	481	0
6	189	9.1	16.8	9.1	15.0	365	2.1	14.5	218	2
7	110	9.0	31.2	10.3	13.9	372	5.1	14.1	289	0
8	131	8.9	25.5	7.5	15.3	335	3.8	13.9	246	1
9	190	6.3	17.7	5.2	15.7	244	1.7	13.2	152	3
10	212	12.5	15.3	13.8	12.3	198	3.2	10.9	153	1
11	271	8.5	12.3	5.9	12.4	195	2.2	7.4	126	3
12	183	22.1	18.2	5.9	9.6	251	3.9	9.6	169	2
13	319	10.8	10.5	6.5	13.8	282	0.7	9.8	102	4
14	187	9.8	17.8	4.8	10.0	261	4.2	9.1	107	2
Mean	190	10.9	19.1							Median
SD	58	3.6	6.3							2

AUC_{0-00}, area under the concentration vs time curve from 0 to infinity; Vd_{ss}, volume of distribution at steady state; Cl_p, total plasma clearance; WBC, white blood-cell count; Hgb, hemoglobin; Plt, platelet count

[a] Toxicity (hematologic) graded according to the Common Toxicity Criteria of the National Cancer Institute

Table 2. Pharmacokinetics and hematologic toxicity of etoposide (400 mg/m^2 as 36-h infusion, single agent) in pretreated patients

Patient number	Diagnosis	$AUC_{0-\infty}$ mg-h/l	Vd l/m^2	Cl_p (ml/min per m^2)	Before therapy:			Nadir counts:			Toxicity[a] grade
					WBC	Hgb	Plt	WBC	Hgb	Plt	
1	SCLC	636	5.8	10.3	9.5	8.9	96	0.5	Transf	37	4
2	AMML	643	3.6	9.5	1.6	10.1	37	0.2	Transf	6	NA
3	ALL	490	3.9	12.8	2.7	13.2	320	0.3	13.3	56	NA
4	Test CA	428	3.3	14.0	9.5	19.2	263	2.4	15.7	200	2
5	Test CA	534	4.0	12.0	3.7	13.5	201	1.8	11.4	189	3
6	NSCLC	497	5.3	13.3	6.6	10.9	325	1.3	9.2	251	3
7	Osteo SA	349	4.1	18.8	8.1	13.5	218	3.2	11.5	129	1
8	Histio SA	355	3.6	17.2	6.4	13.7	261	3.3	11.8	217	1
9	SCLC	441	3.8	12.5	4.5	13.4	232	2.1	10.6	175	2
Mean		486	4.2	13.4							Median
SD		106	0.8	3.0							2

Abbreviations as in Table 1; SCLC, small-cell lung cancer; AMML, acute myelomonocytic leukemia; ALL, acute lymphocytic leukemia; Test CA, testicular cancer; NSCLC, non-SCLC; Osteo SA, osteosarcoma; Histio SA, malignant fibrous histiosarcoma; Transf, transfusion; NA, nonevaluable

Results

Table 1 shows the pharmacokinetic results and the hematologic toxicity of etoposide (200 mg/m^2) given as a 24-h continuous infusion in previously untreated patients with small-cell lung cancer. The nadir counts represent the lowest values observed during the weekly follow-up. The highest grade of toxicity on WBC, hemoglobin, or platelets is reflected in the overall hematologic toxicity grade. The same data were collected for pretreated patients who received single-agent etoposide (400 mg/m^2) as a 36-h continuous infusion (Table 2).

The AUCs, volumes of distribution at steady state (Vd_{ss}), and total plasma clearance rates were tested for their possible correlation to the observed hematologic toxicity. Pearson correlation coefficients are shown in Table 3 for continuous variables, and Spearman correlation coefficients are given in Table 4 for ranked variables.

Significant correlations were found for hematologic values vs AUC or clearance (P values are indicated in parentheses in Tables 3, 4), but not for volume of distribution (data not shown). AUC and clearance were significantly correlated ($P < 0.05$) with WBC or platelet nadirs, but not with the absolute or relative decrease of the counts (Table 3). Conversely, AUC and clearance were significantly correlated with the absolute or relative decrease in hemoglobin, but not with the hemoglobin nadir values. Since AUC and clearance are mathematically related parameters, both were either correlated or not correlated with toxicity, and no obvious discrepancy was observed. Table 4 shows that AUC and clearance were also correlated with the overall grade of hematologic toxicity as well as the grade of leukopenia and thrombocytopenia in patients who had not previously been treated. AUC and clearance were not correlated with the grade of anemia (Table 4).

Table 3. Pearson correlation coefficients for data presented in Table 1 (14 untreated patients)

	AUC	Clearance
WBC nadir	−0.76 (0.002)	0.76 (0.002)
Absolute decrease[a]	0.09 (0.77)	−0.02 (0.94)
Relative decrease	0.49 (0.08)	−0.39 (0.17)
Hgb nadir	−0.47 (0.09)	0.44 (0.12)
Absolute decrease	0.83 (0.0003)	−0.75 (0.002)
Relative decrease	0.84 (0.0002)	−0.76 (0.002)
Plt nadir	−0.70 (0.006)	0.73 (0.003)
Absolute decrease	0.51 (0.06)	−0.54 (0.05)
Relative decrease	0.66 (0.01)	−0.67 (0.009)

Numbers in parentheses represent P values; abbreviations as in Table 1

[a] Absolute decrease = pre- minus posttreatment value; relative decrease = absolute decrease divided by pretreatment value

Table 4. Spearman correlation coefficients for graded hematologic toxicity data from Table 1 (14 untreated patients)

	AUC	Clearance
Leukopenia	0.74 (0.002)	−0.72 (0.004)
Anemia	0.36 (0.20)	−0.38 (0.17)
Thrombocytopenia	0.63 (0.02)	−0.63 (0.02)
Total hematologic toxicity	0.80 (0.0006)	−0.76 (0.002)

Numbers in parentheses represent P values

Table 5. Correlation coefficients for data presented in Table 2 (9 pretreated patients)

	AUC	Clearance
WBC nadir[a]	−0.88 (0.002)	0.86 (0.003)
Plt nadir	−0.63 (0.07)	0.50 (0.17)
Leukopenia grade	0.88 (0.002)	−0.82 (0.007)
Anemia grade	0.64 (0.06)	−0.55 (0.12)
Thrombocytopenia grade	0.49 (0.18)	−0.49 (0.18)
Total hematologic toxicity grade	0.97 (0.0002)	−0.90 (0.006)

Numbers in parentheses represent P values; abbreviations as in Table 1

[a] Pearson correlation coefficients for nadirs and Spearman correlation coefficients for graded toxicity

Table 6. Estimates of regression coefficients and intercepts, standard errors of estimates, and estimates of Pearson and Spearman correlation coefficients of the AUC and total plasma clearance on various measures of hematologic toxicity for 14 untreated patients

Dependent variable	Intercept[a]	Slope[a]	$r_{Pearson}$[b]	$r_{Spearman}$[b]
AUC:				
WBC nadir	4.03 (0.42)	−0.01 (0.003)	−0.71 (0.004)	−0.80 (0.0006)
WBC relative decrease	42.11 (8.15)	0.13 (0.05)	0.58 (0.03)	0.64 (0.02)
Plt nadir	297.47 (36.54)	−0.77 (0.24)	−0.68 (0.007)	−0.74 (0.003)
Plt relative decrease	17.19 (8.14)	0.14 (0.05)	0.62 (0.02)	0.70 (0.006)
Log Plt relative decrease	2.98 (0.27)	0.004 (0.002)	0.57 (0.04)	0.66 (0.02)
Hgb relative decrease	−1.55 (3.11)	0.11 (0.02)	0.84 (0.0002)	0.86 (0.0001)
Log Hgb relative decrease	1.22 (0.47)	0.008 (0.003)	0.68 (0.02)	0.78 (0.005)
Clearance:				
WBC nadir	0.27 (0.82)	0.16 (0.04)	0.76 (0.002)	0.77 (0.001)
Plt nadir	−46.45 (70.56)	13.25 (3.53)	0.73 (0.003)	0.71 (0.004)
Plt relative decrease	82.17 (16.07)	−2.50 (0.80)	−0.67 (0.009)	−0.74 (0.003)
Log Plt relative decrease	4.93 (0.44)	−0.08 (0.02)	−0.73 (0.005)	−0.71 (0.007)
Hgb relative decrease	41.63 (7.78)	−1.58 (0.39)	−0.76 (0.002)	−0.83 (0.0002)
Log Hgb relative decrease	5.22 (1.05)	−0.17 (0.06)	−0.69 (0.02)	−0.75 (0.009)

Abbreviations as in Table 1; *r*, correlation coefficient
[a] Numbers in parentheses represent standard errors
[b] Numbers in parentheses represent *P values*

Table 7. Estimates of regression coefficients and intercepts, standard errors of estimates, and estimates of Pearson and Spearman correlation coefficients of the AUC and total plasma clearance on various measures of hematologic toxicity for 9 pretreated patients

Dependent variable	Intercept[a]	Slope[a]	$r_{Pearson}$[b]	$r_{Spearman}$[b]
AUC:				
WBC nadir	6.46 (0.57)	0.009 (0.001)	−0.96 (0.0005)	−0.93 (0.003)
WBC relative decrease	14.93 (27.47)	0.11 (0.06)	0.76 (0.12)	0.43 (0.34)
Log WBC relative decrease	3.46 (0.42)	0.001 (0.0009)	0.73 (0.15)	0.43 (0.34)
Plt nadir	390.78 (119.87)	−0.52 (0.24)	−0.63 (0.07)	−0.47 (0.21)
Plt relative decrease	−29.06 (43.24)	0.14 (0.09)	0.53 (0.15)	0.32 (0.41)
Clearance:				
WBC nadir	−2.14 (0.95)	0.30 (0.07)	0.90 (0.006)	0.86 (0.01)
Plt nadir	−54.89 (130.9)	14.56 (9.57)	0.50 (0.17)	0.60 (0.09)

Abbreviations as in Tables 1 and 6
[a] Numbers in parentheses represent standard errors
[b] Numbers in parentheses represent *P* values

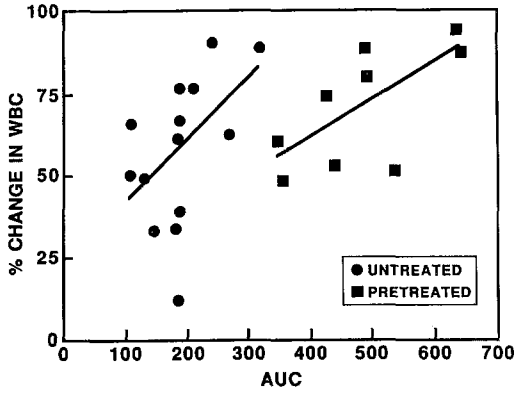

Fig. 1. Percentage of change in white blood cells (*% change in WBC*) plotted against the AUC for etoposide in patients who were not previously treated (*untreated*, $n = 14$) and those who had received previous chemotherapy (*pretreated*, $n = 9$)

For the group of pretreated patients, the correlation coefficients are presented in Table 5 for the WBC and platelet nadirs as well as the grades of leukopenia, anemia, and thrombocytopenia and the overall hematologic toxicity. Other correlation coefficients were not significant and were excluded from Table 5. Significant correlations were observed for the toxicity on WBC (nadir and grade) and overall hematologic toxicity.

The regression equations found in the parametric analyses are reported in Tables 6 and 7 for significant pairings. The correlation coefficients for relative decreases in hematologic variables were always more significant than those for absolute decreases; therefore, only data for relative decreases are given in Tables 6 and 7.

The plots for all relationships between pharmacokinetic and hematologic variables were reviewed. Representative graphs for AUC vs the percentage of change in WBC, hemoglobin, and platelets are shown in Figs. 1–3. The correlation analyses for Tables 3–5 and Figs. 1–3 implicitly used a linear relationship between variables or the ranks of variables. To account for a possible curvilinear fit, the relationships between pharmacokinetic variables and the log of hematologic variables were also computed. Although curvilinear relationships were linearized, the va-

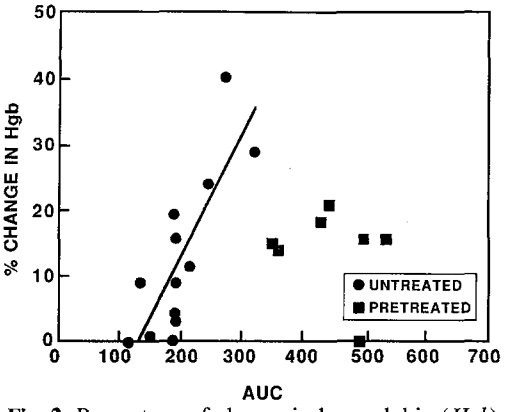

Fig. 2. Percentage of change in hemoglobin (*Hgb*) plotted against the AUC as in Fig. 1

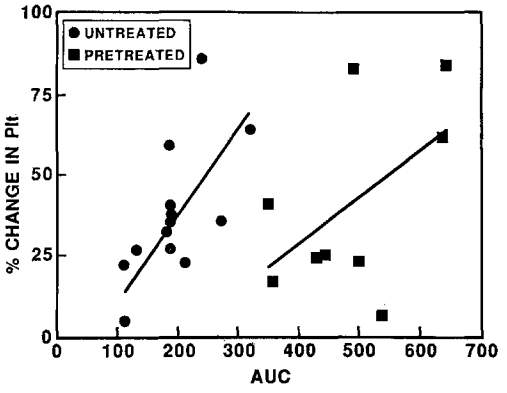

Fig. 3. Percentage of change in platelets (*Plt*) plotted against the AUC as in Fig. 1

riability increased, thereby reducing the correlation coefficients. Examples of the relationship between the log relative decrease in hematologic variables vs AUC or clearance are shown in Tables 6 and 7.

Discussion

The major and dose-limiting toxicity of etoposide is known to be myelosupression, specifically leukopenia, anemia, and thrombocytopenia. Pharmacokinetic values are also known to vary widely from patient to patient despite a uniform dosage based on body surface area. The hypothesis was that it is not the dosage but rather a pharmacokinetic measure of the interpatient difference in drug exposure (i.e., AUC) or a determinant of exposure (i.e., clearance) that predicts for hematologic toxicity.

The present study found this hypothesis to be true, demonstrating significant correlations between pharmacokinetic variables (AUC and clearance) and the ensuing hematologic toxicity. This relationship existed for previously untreated vs pretreated patients (although the second group was small) and demonstrated for the combination of etoposide and cisplatin as well as etoposide monotherapy. Our findings confirm previous work by Bennett et al. [1] and Ratain et al. [7], who published similar correlations for leukopenia. Moreover, in the present study, anemia and thrombocytopenia were also correlated with the varying degree of drug exposure represented by AUC or clearance.

The individual values for AUC and clearance varied widely (Tables 1, 2) and were correlated with WBC nadir counts, the decrease in platelets, platelet nadir, and the decrease in hemoglobin (Tables 3, 5). When an accepted grading system for hematologic toxicity was applied (Common Toxicity Criteria of the NCI), the grade of leukopenia and the composite total grade of leukopenia/anemia/thrombocytopenia were found to be related to AUC and clearance (Tables 4, 5).

This study and others [1, 7] have observed that large interpatient variability in drug disposition is the likely basis for the variable degree of toxicity. Thus, cumulative evidence suggests that pharmacokinetic monitoring with drug measurements should be useful in identifying patients at risk of developing severe hematologic toxicity. Figures 1–3 provide a graphic representation of the relationship between the percentage of change in hematologic variables and a measure of drug exposure (AUC). The results are concordant with those of Ratain et al. [7] and suggest that a proportion of the variance in the outcome variables is not described by a linear relationship between toxicity and exposure to total drug concentrations. The analyses of pharmacokinetic variables vs the log of hematologic variables did not yield correlation coefficients that were superior to those of linear analyses (Tables 6, 7). At least in patients with abnormal organ function (i.e., high bilirubin, low albumin), it may be necessary to measure the nonprotein-bound fraction of etoposide as well as the total drug concentration [11].

A remaining problem pertains to the optimal schedule of etoposide that produces a clinical tumor response. The present and previous pharmacodynamic studies [1, 7, 8] have used continuous-infusion regimens. Etoposide is a highly effective agent in small-cell lung cancer, but it is also highly schedule-dependent. Recently reported phase III trials [9, 12] have shown that the combination of etoposide and cisplatin is as effective as the combination of cyclophosphamide, doxorubicin, and vincristine. The present study failed to demonstrate a correlation between pharmacokinetic parameters and tumor response in patients with small-cell lung cancer (data not shown). Clark et al. [2] have recently addressed the schedule dependence of etoposide and found that a 24-h continous-infusion regimen (response rate, 10%) was inferior to five or eight consecutive, daily 2-h infusions (response rate, 72%–90%).

The continuous-infusion regimen of the current study was therefore abandoned in favor of a daily, short-term infusion schedule, with the intent of correlating pharmacokinetic parameters not only with toxicity but also with tumor response. The value of a large AUC or slow clearance for predicting toxicity will be tested prospectively.

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