Cancer Chemother Pharmacol (1992) 31: 161–166

Cancer Chemotherapy and Pharmacology

Pharmacodynamics of three daily infusions of etoposide in patients with extensive-stage small-cell lung cancer

Antonius A. Miller[1,2], Elizabeth A. Tolley[3], Harvey B. Niell[1,2], Clinton F. Stewart[4], and John P. Griffin[5]

[1] Veterans Affairs Medical Center, and [2] Division of Hematology/Oncology, Department of Medicine, [3] Department of Biostatistics and Epidemiology, [4] Department of Clinical Pharmacy, [5] Division of Pulmonary Medicine, Department of Medicine, University of Tennessee, Memphis, TN, USA

Received 24 October 1991/24 June 1992

Summary. The objectives of this study were to define the pharmacodynamics of etoposide and to develop potentially useful models (1) to estimate the plasma clearance using a limited number of samples and (2) to describe the relationship between clearance and the dose-limiting toxicity. A total of 17 patients with extensive-stage small-cell lung cancer were treated with 150 mg/m^2 etoposide daily for 3 consecutive days and with 100 mg/m^2 cisplatin on day 3 only. Both drugs were given intravenously over 1 h. Treatment was repeated every 21 days for up to six courses. All patients were newly diagnosed (no previous chemotherapy or irradiation) and had a performance status of 0–2. Six patients achieved a complete response as confirmed by repeat bronchoscopy and five patients showed a partial response, for an overall objective response rate of 65% (95% confidence interval, 38%–87%). The median survival was 8 months (range, 1–24+ months). The dose-limiting toxicity was neutropenia. Etoposide pharmacokinetics were measured during the first course and determinations were repeated during courses 3 or 4 and 6. Complete blood counts were obtained weekly. Correlations for etoposide clearance and hematologic toxicities were evaluated for 17 initial courses and for an overall number of 33 courses. Pharmacodynamic correlations were significant for graded hematologic toxicities, as well as nadirs of leukocytes, neutrophils, and platelets for the initial courses and for all courses. To reduce the requirement for numerous blood samples, a limited sampling model was developed to estimate the area under the concentration versus time curve (AUC) with the following equation:

$$AUC = 15.45+3.86 \times C_2+7.10 \times C_4,$$

where C_2 and C_4 represent the etoposide concentrations at 2 and 4 h, respectively. The total plasma clearance was calculated as the dose divided by the AUC; correlations with toxicity were better for clearance expressed in milliliters per minute than for that expressed in milliliters per minute per square meter of body surface area. The absolute neutrophil count at the nadir (ANC_n) can be estimated by the following pharmacodynamic model, which is based on 33 courses:

$$ANC_n = -0.399+0.024 \times E_{cl},$$

where E_{cl} represents the etoposide clearance expressed in milliliters per minute. Further studies are necessary to validate both models prospectively.

Introduction

Etoposide in combination with cisplatin is effective in treating patients with small-cell lung cancer [4]. A dose-response relationship exists for etoposide as for other cytostatic agents, although very high doses have not been shown to be more effective than standard doses in extensive-stage small-cell lung cancer [3, 5]. The variability of drug effects (toxicity and tumor response) in a population of patients who have all received the same dose as calculated in milligrams per square meter of body surface area is a clinical reality. Recent evidence suggests that the variability observed in drug disposition despite the uniform dosage is responsible for the variable clinical outcome [6, 8]. This pharmacokinetics-response (rather than dose-response) relationship or the pharmacodynamics in cancer therapy merits further investigation, as has recently been reviewed by Ratain et al. [7].

In a previous study [6], the pharmacodynamic results of continuous-infusion etoposide have been described. The pharmacokinetic variables of the area under the curve (AUC) or drug clearance were significantly correlated with the degree of hematologic toxicity. Ratain et al. [8], who had previously shown that leukopenia is a function of etoposide concentrations during continuous infusion, have

This work was supported by a merit review grant from the Department of Veterans Affairs, Washington, D. C.

Correspondence to: A. Miller, University of Tennessee, 3 North Dunlap, Memphis, TN 38163, USA

successfully used a dose-modification scheme based on drug measurements to individualize dose intensity.

Slevin et al. [9] reported that a 24-h continuous-infusion regimen was inferior to a daily short-infusion schedule in patients with small-cell lung cancer. Therefore, the present study was undertaken to define the pharmacodynamics of etoposide given intravenously over 1 h on 3 consecutive days. On day 3, cisplatin was given with the etoposide. The objective was to correlate etoposide plasma clearance with the resulting hematologic toxicity. If this could be accomplished, the secondary objective was to develop both a model to reduce the need for numerous blood samples and a model describing the relationship between the clearance and the most severe toxicity encountered.

Patients and methods

Patient selection. Patients over 18 years of age with histologically proven, extensive-stage, measurable or evaluable small-cell lung cancer were eligible for this study. Staging procedures included a chest X-ray, fiber-optic bronchoscopy, computer-assisted tomography of the chest and upper abdomen (liver, adrenals), bone scan, bone marrow biopsy (bilateral iliac crest), and computer-assisted tomography of the brain. A performance status of 0–2 (Eastern Cooperative Oncology Group scale) was required. No prior chemotherapy or irradiation was allowed. Patients with other previous or concomitant malignancies and other serious medical or psychiatric diseases were excluded. Laboratory criteria for entry on the protocol included a WBC of $\geq$4,000/μl, a hemoglobin level of $\geq$10 g/dl, a platelet count of $\geq$100,000/μl, a serum creatinine value of <2 mg/dl, creatinine clearance of >60 ml/min, a blood urea nitrogen (BUN) level of <1.5 times the normal value, and a bilirubin level of <1.5 times the normal value. The protocol was approved by the Human Studies Committee at the Veterans Affairs Medical Center, and all patients signed a consent form.

Treatment plan. Etoposide was given as a 1-h infusion at a dose of 150 mg/m^2 daily on 3 consecutive days. On day 3 only, 100 mg/m^2 cisplatin was infused over 1 h together with etoposide. Hydration before cisplatin administration consisted of 2 l normal saline given intravenously over 24 h. Mannitol was used as a diuretic. Metoclopramide, diphenhydramine, or ondansetron was given as needed to control nausea and vomiting. Treatment was repeated every 21 days for up to six courses. Before every course, complete blood counts (CBC) with differential, electrolyte values (including calcium and magnesium), liver- and renal-function chemistries, determinations of lactate dehydrogenase levels as well as of total protein and albumin, and a chest X-ray were obtained. While on the treatment protocol, patients were seen once a week in the clinic for CBC and toxicity follow-up. Subsequent treatment was delayed for 1 week for granulocyte counts of <1,500/μl, and then patients were treated at the 100% dose level. No dose adjustment was made for low nadir counts so as not to compromise the dose intensity in this chemoresponsive tumor. Patients were evaluated for tumor response after they had completed two and six courses. Non-responders were taken off study. All patients were followed for survival.

Etoposide pharmacokinetics. Pharmacokinetic sampling was performed during course 1 in all patients and in courses 3 or 4 and 6 in patients responding to treatment. Blood samples (5–7 ml) were collected in heparinized tubes at the following time points: day 1, before the etoposide infusion and at 0, 1, 4, 7, and 23 h after the infusion; day 2, at the end of the infusion and 23 h later; day 3, at 0, 0.083, 0.25, 0.5, 0.75, 1, 2, 4, 6, 24, and 48 h after the infusion. The 23-h samples were obtained just before the next infusion. The samples were immediately placed on ice and centrifuged, and the plasma was transferred and stored frozen until analysis. Plasma was analyzed for total and free (not bound to plasma proteins) concentrations of etoposide. A previously described extraction procedure was used [6]. Briefly, 1 ml plasma was extracted over disposable silica C18 columns with 2×1 ml 2:1 (v:v) chloroform: acetonitrile. The eluant was dried under a stream of nitrogen and reconstituted with 0.1 ml 60:40 (v:v) water: acetonitrile for high-performance liquid chromatography (HPLC). Plasma was also processed by equilibrium dialysis as previously described [11] or by ultrafiltration through a micropartition system equipped with a YMT membrane (Amicon, Danvers, Mass.) for measurement of the free drug. Equilibrium dialysis and ultrafiltration gave similar results. For the dialysis method, tritiated etoposide was added and the concentration was calculated after liquid scintillation counting as described elsewhere [11]. After ultrafiltration, the resulting filtrate was injected on to the HPLC column. The HPLC system (Waters Chromatography, Milford, Mass.) consisted of a WISP cooled automatic injector, an M510 pump, a micro-Bondapak phenyl column, an M490 UV detector set to 233 nm, and Baseline software on a CompuAdd 286 computer. The mobile phase was 62:37:1 (by vol.) water: acetonitrile: glacial acetic acid. Details of the HPLC methods used have been described elsewhere [6]. The HPLC detection limit for etoposide was 0.1 μg/ml.

An open two-compartment model was used to fit the concentration versus time data for each patient. Pharmacokinetic values were calculated using the PCNONLIN computer program (version 3.0, model 10) from Statistical Consultants Inc. (Lexington, Ky.).

Clinical outcome evaluation. Complete blood counts were recorded weekly to estimate nadir counts, the absolute decrease (pretreatment minus nadir counts) and relative decrease (absolute decrease divided by pretreatment counts) in counts, and the survival fraction (nadir divided by pretreatment counts). Hematologic and any other toxicities were graded according to the Common Toxicity Criteria established by the National Cancer Institute. Clinical response was evaluated after two and six courses according to standard WHO criteria. Patients who were in clinical complete remission after six courses underwent repeat bronchoscopy. Survival was calculated from the time of enrollment in the study.

Biostatistics. A variety of statistical techniques were used to evaluate the pharmacodynamics of infusional etoposide. For each course, correlation analysis yielded estimates of correlation coefficients for etoposide clearance and observed toxicities. Pearson correlation coefficients were obtained for continuous variables (i.e., blood counts) and Spearman correlation coefficients were obtained for variables related to graded toxicity. Because patients could have received more than one treatment course (i.e., lack of independence), partial correlation coefficients were estimated after adjustments for patients and courses. To determine whether there was evidence of cumulative toxicity, the effects of the treatment course on pretreatment and nadir blood counts and drug concentrations were assessed after adjustments for differences between patients using two-way analysis of variance. To determine whether the tumor response would affect survival, patients were stratified according to tumor response (i.e., yes/no) and Kaplan-Meier estimates of the survival distribution were computed within each stratum and tested for equality. In the survival analysis, the pretreatment albumin concentration and performance status were included as confounding variables; potential covariates, based on the first course only, included pharmacokinetic parameters and clinical indicators of hematotoxicity: the AUC for total drug, the AUC for unbound drug, clearance (measured in milliliters per minute and in milliliters per minute per square meter of body surface area), and nadir for the absolute count and survival fraction of granulocytes. Covariates and confounders were tested individually and jointly for their association with survival. Finally, inter- and intrapatient variabilities of drug clearance were estimated by the components of variance model [10]. The interpatient variability of drug clearance (variation in average drug clearance between patients) was also expressed as a coefficient of variation. Likewise, coefficients of variation were calculated for each patient.

To develop a limited sampling model that would be clinically relevant, it appeared important to test whether data from all patients and courses were independent. Because some patients received multiple courses, the following analyses were done. First, using data from all patients and courses in five separate, simple linear regression analyses, the AUC value was regressed on concentrations at 0, 1, 2, 4, 6, or 24 h

Table 1. Patients' characteristics and tumor response

Patients entered	17
Median age	62 (range, 37–70) years
Median performance status	1 (range, 0–2)
Median serum albumin	3.6 (range, 2.8–4.2) g/dl
Treatment courses	76 (median per patient, 6; range, 1–6)
Complete response	6
Partial response	5
Stable disease	2
Progressive disease	4
Objective response rate	65%
95% Confidence intervals	38%–87%
Median survival	8 (range, 1–24+) months

after adjustment for differences among patients. The patient was not a statistically significant source of variation ($P > 0.4$) at 1, 2, 4, or 6 hours; therefore, there was no evidence of bias on account of the assumption of independence. For the AUC of total drug, the proportion of interpatient variation ranged from 44% to 53% and the proportion for intrapatient variation ranged from 47% to 56%. For the analysis using the concentration at 24 h as the independent variable, the patient was a significant source of variation; the concentration at 24 h was no longer considered a potential predictor because a lack of independence was detected. Second, the intercept and slope from each univariate prediction equation estimated after adjustment for differences between patients was compared with those obtained by ignoring multiple courses. No significant difference was detected among estimates of intercepts or slopes for 1, 2, 4, or 6 h. Since patients who received multiple courses behaved statistically as if they had independent observations, the limited sampling model shown in Eq. 1 of the Results section was based on all available data.

The following strategy was used to identify the optimal sampling times required to obtain accurate estimates of the AUC. For each simple linear regression analysis, results included a univariate prediction equation, a coefficient of determination (r^2), a correlation coefficient (r), the mean predicted AUC, and the mean and standard deviation for the prediction errors. An optimal sampling model was identified by fitting a multiple linear regression model to the complete data set using a stepwise algorithm, with the concentration at 1, 2, 4, and 6 h being included as potential predictors. A significance level of 0.05 was set for both inclusion and elimination of variables. Results included a prediction equation with more than one predictor, a coefficient of determination (R^2), a multiple correlation coefficient (R), the mean predicted AUC, and the mean and standard deviation for the prediction errors. These results were compared with those obtained using the best univariate predictor. Validation of the multiple regression model involved dividing the data of consecutive patients into training and test sets of 17 courses in 10 patients and 16 courses in 7 patients, respectively; the training set contained the first 10 patients enrolled in the study, whereas the patients enrolled subsequently comprised the test set. For the test set, the prediction error was also expressed relative to the patients's AUC value.

A linear model was employed to describe the pharmacodynamic drug-response relationship. Specification of the theoretical model was based on the following assumption about the pharmacodynamic relationship: the hematologic toxic effect of the drug at a particular clearance, E_{Cl}, is directly proportional to the amount of effect. Estimates of the parameters were obtained from these data using the following statistical model:

$$\text{Count}_n = \alpha + \beta \times E_{Cl} + \varepsilon.$$

Estimates of parameters (α and β) are unbiased if the model is correctly specified, and errors in the predictor variables are random and independent of the response [2]. Visual examination of residual plots were used to check the basic regression assumptions and to detect evidence of bias [2]. The average prediction error was estimated by the root mean square error.

Table 2. Toxicity

Courses with nadir count	75 (incomplete weekly follow-up, 1)
Median nadirs:	
WBC	2.6 (range, 0.2–5.3) $\times 10^3/\mu l$
Granulocytes	0.8 (range, 0.01–3.1) $\times 10^3/\mu l$
Hemoglobin	9.1 (range, 7.1–13.6) g/dl
Platelets	137 (range, 9–369) $\times 10^3/\mu l$
Granulocytopenia:	
Grade 2	15 courses, 7 patients
Grade 3	27 courses, 11 patients
Grade 4	23 courses, 13 patients
Neutropenic fever:	
Grade 2	1 course, 1 patient
Grade 3	2 courses, 2 patients
Grade 4	1 course, 1 patient
Median grade for:	
Anemia	2 (range, 0–3)
Thrombocytopenia	1 (range, 0–4)
Nausea/vomiting	1 (range, 0–3)
Renal toxicity	0 (range, 0–3)
Alopecia	All patients
Neurosensory toxicity:	
Grade 1	2
Grade 2	2
Diarrhea:	
Grade 2	2

Results

Response and toxicity

A total of 17 patients were enrolled on the protocol and all were evaluable. The patients' characteristics and tumor response are shown in Table 1. Six patients achieved a complete clinical remission that was confirmed by repeat bronchoscopy. Responders survived significantly longer ($P < 0.05$) as determined using log-rank and Wilcoxon tests, but this cannot be taken as evidence of treatment efficacy [1]. None of the covariates was significant; these included albumin, pharmacokinetic parameters, and toxicity parameters.

In all, 76 treatment courses were given, and in 75 courses, weekly follow-up data were available for blood counts. The treatment-associated toxicities are presented in Table 2. Dose adjustments were made in only two patients. One patient developed renal toxicity of grades 1, 2, and 3 during courses 1, 2, and 3, respectively, and received no further cisplatin. The other patient developed grade 4 granulocytopenia, grade 3 anemia, and grade 1 renal toxicity after course 4 and received therapy at the 75% dose level for etoposide and cisplatin in courses 5 and 6.

Etoposide pharmacokinetics

The pharmacokinetic results for the 17 initial treatment courses are shown in Table 3. The peak and trough concentrations after drug administration on days 1, 2, and 3 did not significantly differ. The concentration versus time

Table 3. Etoposide pharmacokinetics

AUC	119 ± 33 μg ml^{-1} h
Drug not bound to protein	11% ± 1.9%
AUC, unbound drug	13 ± 3.8 μg ml^{-1} h
Total plasma clearance	22 ± 6.3 ml min^{-1} m^{-2}
Total plasma clearance	44 ± 14 ml/min
Clearance, unbound drug	422 ± 181 ml/min

Data represent mean values ± SD for 17 initial treatment courses

curves for days 1 and 3 were superimposable. No drug accumulation from day 1 to day 3 was apparent. Etoposide kinetics were not altered by cisplatin coadministration on day 3. The AUC resulting from the etoposide dose of 150 mg/m^2 on day 3 of course 1 is given in Table 3. The fraction of the drug not bound to protein (mean value ± SD in Table 3; median, 13%; range, 7%–19%) was measured for each patient and the AUC for free drug was calculated. The variability in AUC (free drug) correlated with the variability in serum albumin concentrations (Pearson correlation) coefficient, –0.57; $P < 0.05$). A lack of relationship between body surface area and clearance was demonstrated by Ratain et al. [8] and confirmed in this study. Therefore, in Table 3 clearance is expressed in milliliters per minute per square meter of body surface area and in milliliters per minute.

The interpatient variance in drug clearance (81%) was substantially greater than the intrapatient variance (19%). Expressed as coefficients of variation, the interpatient variability in clearance was 34% and the intrapatient variability in patients who received at least 2 treatment courses ($n = 11$) ranged from 2% to 24% (median, 13%).

Etoposide pharmacodynamics

The results for correlations between the plasma clearance of etoposide and hematologic toxicities is shown in Table 4. Drug clearance was significantly correlated with the hematologic toxicities in course 1, except for hemoglobin, for which only the graded variable was significant. When all courses were taken into account, the correlations remained significant for graded toxicity and nadir counts. As compared with the results of the first course only, the associations between clearance and hematologic toxicities were less close when all courses were included; closer examination revealed evidence of cumulative toxicity with multiple courses. After adjustments for patients and courses, only the partial correlation of the nadir of the absolute neutrophil count with clearance was significant ($P < 0.02$).

Clearance is defined as the dose divided by the AUC. Clearance can be expressed in milliliters per minute or in milliliters per minute per square meter of body surface area, depending on whether the total dose in milligrams or the dose in milligrams per square meter of body surface area is used for this calculation. Table 5 shows the correlations between the pharmacokinetic variables and the dose-limiting toxicity against the neutrophils. Correlations for clearance expressed in milliliters per minute were stronger than those for clearance expressed in milliliters per square meter of body surface area. Correlation coefficients were highest for AUC or clearance of unbound drug. All relationships were found to be linear. The correlations between kinetic parameters of etoposide and tumor response or survival were not statistically significant. Cisplatin may have confounded these correlations.

Table 4. Etoposide plasma clearance in ml/min in correlation to hematologic toxicities

Variable	First course only ($n = 17$)		All courses ($n = 33$)	
	Correlation coefficient	P value	Correlation coefficient	P value
Graded WBC toxicity	–0.57	0.02	–0.31	0.08
Graded granulocytopenia	–0.77	0.0003	–0.50	0.004
Graded anemia	–0.55	0.02	–0.38	0.04
Graded thrombocytopenia	–0.64	0.006	–0.48	0.005
WBC nadir	0.59	0.02	0.36	0.04
Granulocyte nadir	0.86	0.0001	0.46	0.009
Hemoglobin nadir	0.30	0.3	0.25	0.2
Platelet nadir	0.65	0.006	0.43	0.02
WBC survival fraction	0.61	0.009	0.19	0.3
Granulocyte survival fraction	0.85	0.0001	0.24	0.2
Hemoglobin survival fraction	0.25	0.3	0.15	0.4
Platelet survival fraction	0.55	0.03	0.10	0.6
WBC, absolute decrease	–0.43	0.09	–0.15	0.4
Granulocyte, absolute decrease	–0.43	0.09	–0.14	0.4
Hemoglobin, absolute decrease	–0.14	0.6	–0.05	0.7
Platelet, absolute decrease	–0.25	0.3	–0.11	0.5
WBC, relative decrease	–0.61	0.009	–0.19	0.3
Granulocyte, relative decrease	–0.85	0.0001	–0.25	0.2
Hemoglobin, relative decrease	–0.25	0.3	–0.14	0.4
Platelet, relative decrease	–0.55	0.03	–0.12	0.5

The Spearman correlation coefficient was used for graded variables and the Pearson correlation coefficient was used for all other variables

Table 5. Etoposide pharmacodynamics during the first course in 17 patients

Kinetic variable	Absolute neutrophil count	
	Nadir	Survival fraction
AUC, total drug	–0.71 (0.001)	–0.65 (0.005)
AUC, unbound drug	–0.97 (0.0001)	–0.90 (0.0001)
Total clearance (ml min^{-1} m^{-2})	0.77 (0.0003)	0.72 (0.001)
Total clearance (ml/min)	0.86 (0.0001)	0.85 (0.0001)
Clearance, unbound drug[a]	0.92 (0.0001)	0.94 (0.0001)

Data represent correlation coefficients; *P* values are shown in parentheses

[a] Expressed in ml/min

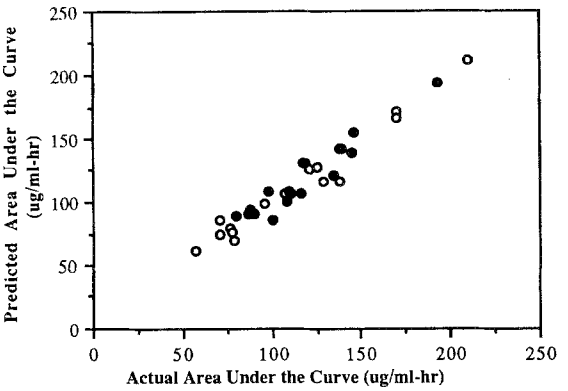

Fig. 1. Actual area under the curve plotted against the predicted area under the curve for training data (○——○) and test data (●——●) sets

Limited sampling model

For the calculation of drug clearance, the AUC value must be known. For estimations of AUC based on fewer sampling points, a limited sampling model was developed. Of all the sampling points used in this study, the AUC could be best estimated on the basis of the drug concentrations at 2 and 4 h. If the etoposide concentrations at 2 (C_2) and 4 h (C_4) are known, the AUC can be estimated as follows:

$$AUC = 15.45+3.86 \times C_2+7.10 \times C_4. \quad (1)$$

The AUC in this equation was for total drug expressed in micrograms per milliliter times hour, and C_2 and C_4 were expressed in micrograms per milliliter. The parameter estimates ±SE were as follows: intercept, 15.45±4.79 (P = 0.003); C_2, 3.86±0.80 (P = 0.001); and C_4, 7.10±1.23 (P = 0.001). The R^2 for the multivariate model with the two concentrations was 0.94. The root mean square error was 8.8 μg ml^{-1} h. The mean predicted AUC was 116 μg ml^{-1} h, with the standard deviation being 35 μg ml^{-1} h and the coefficient of variation, 7.6%. The univariate model for one concentration at 4 h had an r^2 of 0.90, with the root mean square error being 11.6 μg ml^{-1} h. For all other univariate models for one concentration time point, r^2 was <0.90.

For a preliminary assessment of the predictive performance of the model, the data were divided into a training set of 17 courses and a test set of 16 courses. For the training set the following equation was found: AUC = 13.75 +3.75 × C_2+7.45 × C_4, with an R^2 of 0.96 and a root mean square error of 9.3 μg ml^{-1} h. For the test set, the mean predicted AUC (± SD) was 116±29 μg ml^{-1} h. The mean prediction error (bias) was 0.15 μg ml^{-1} h. The root mean square error (precision) was 8.7 μg ml^{-1} h, which was 7.5% of the mean actual AUC. The plot of the actual AUC versus the predicted AUC is shown in Fig. 1.

Multivariate analysis also showed that the AUC of unbound drug can best be estimated by concentration time points at 2 and 4 h as follows:

$$AUC_{(free\ drug)} = 3.65+0.41 \times C_2+0.46 \times C_4. \quad (2)$$

Because the R^2 for this model was only 0.75, the remainder of the statistical analysis for this equation is not shown.

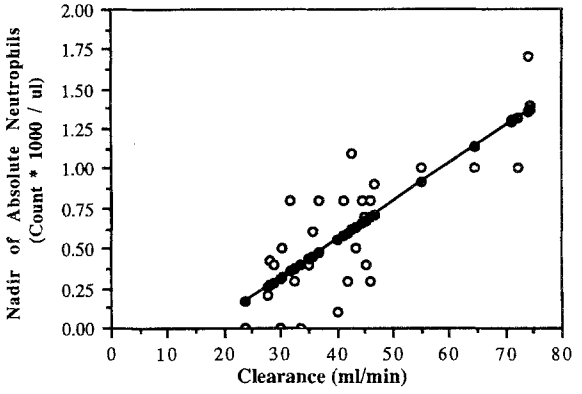

Fig. 2. Observed clearance plotted against the predicted (●——●) and actual (○——○) nadirs of the absolute neutrophil count for 33 treatment courses

Pharmacodynamic model

A pharmacodynamic model was developed to describe the relationship between the etoposide clearance and the resulting leukocyte (WBC) and neutrophil (ANC) nadirs. If the etoposide clearance (E_{cl}) is known, the nadirs (WBC_n, ANC_n) can be estimated as follows:

$$WBC_n = -0.057+0.048 \times E_{cl} \text{ and} \quad (3)$$
$$ANC_n = -0.565 +0.024 \times E_{cl} \quad (4)$$

In all equations, the count × 10^3 per microliter was used. Clearance was expressed in milliliters per minute. The estimates for the intercept (a) and the slope (b) ±SE and the 95% confidence intervals (CI) were as follows: WBC: a = –0.057±0.782 (CI, –1.724, 1.610), b = 0.048 ±0.017 (CI, 0.012, 0.084); and ANC: a = –0.565±0.170 (CI, –0.927, –0.203), b = 0.024±0.004 (CI, 0.015, 0.033). The r^2 for the WBC_n equation was 0.34. The r^2 for the ANC_n equation was 0.74, with P values for a and b being 0.005 and 0.0001, respectively. Therefore, etoposide clearance is more strongly related to toxicity against the neutrophils than to toxicity against the total white blood cells. The average prediction errors for WBC_n and ANC_n were 0.957 and 0.208 × 10^3/μl, respectively.

The above equations for the pharmacodynamic model were based on data from the first treatment course in each patient ($n = 17$). If all courses with pharmacodynamic data ($n = 33$) were used, the following equation was found:

$$ANC_n = -0.399 + 0.024 \times E_{cl}. \quad (5)$$

The r^2 for this equation was 0.65, and the standard errors for a and b were 0.15 and 0.003, respectively. The average prediction error was $0.260 \times 10^3/\mu l$. The actual and predicted ANC_n values for the range of clearances observed in this study are shown in Fig. 2. An attempt was made to include albumin concentration, performance status, or pretreatment count into the pharmacodynamic model, but no statistical improvement was apparent.

Discussion

As for other drugs used in internal medicine (i.e., aminoglucosides, digoxin, theophylline, and dilantin, among others), it appears clinically important to define therapeutic drug concentrations or clearance ranges so as to avoid or limit toxicity. Although the therapeutic range of cytostatic drugs is generally narrower than that of other drugs, progress in this area has been slow [7]. This may be due to the unique dosing regimens used in medical oncology, whereby drugs are often given in cycles rather than continuously. Pharmacokinetics during a cycle are more difficult to assess than are steady-state drug levels on chronic regimens.

Previous studies of 24- [6], 36- [6], or 72-h [8] continuous-infusion etoposide have demonstrated correlations between variables of etoposide exposure and leukopenia. The AUC [6], clearance [6], or 24-h steady-state levels [8] of etoposide were used to estimate drug exposure. Ratain et al. [8] developed a dose-modification scheme based on the concentration of etoposide at 24 h during infusion. Stewart et al. [12] also found a relationship between systemic exposure to etoposide and hematologic toxicity; the toxicity correlated better with the AUC of unbound etoposide than with that of the total drug.

The current report confirms these previous findings [6, 8, 12] of a relationship between exposure to etoposide and the resulting hematologic toxicity. Etoposide plasma clearance was used in this study as the predictor variable. The outcome variable that most clearly correlated with clearance was neutropenia expressed as graded toxicity, nadir count, or survival fraction (Tables 4, 5). The most severe toxicity of all the adverse effects encountered during this study was also neutropenia (Table 2). Clinically it may be useful to predict neutropenia because it may result in febrile episodes or sepsis.

It therefore appears that the development of models that estimate clearance (limited sample model) and nadir neutrophil counts (pharmacodynamic model) may have clinical applications. These models are presented herein, but they must now be validated prospectively before further clinical conclusions can be drawn. The prospective evaluation of prediction models may improve our ability to quantify pharmacodynamic relationships and may ultimately result in more routine use of model-based dosing.

The response rate obtained in this trial (Table 1) compares favorably with other reports [4]. No correlation could be shown between pharmacokinetic values of etoposide and tumor response or survival. This may have been due to the small number of observations, to other variables within the tumor that determine response, or to the contributions of cisplatin used in combination with etoposide. In a future trial, the continuous pharmacokinetic variables will also be compared with absolute measurements of tumor mass and response in centimeters rather than with only the conventional groups of response or progression.

Acknowledgements. The authors appreciate the assistance of Ms. B. Knowles in laboratory analyses and of Ms. K. Kelley in data acquisition and thank Ms. B. Eckles for typing the manuscript.

References

1. Anderson JR, Cain KC, Gelber RD (1983) Analysis of survival by tumor response. J Clin Oncol 1: 710
2. Draper NR, Smith H (1981) Applied regression analysis, 2nd edn. John Wiley and Sons, New York, p 141
3. Ihde DC, Mulshine JL, Kramer BS, Steinberg SM, Edison M, Phelps R, Lesar M, Phares JC, Minna JD, Johnson BE (1991) Randomized trial of high vs standard dose etoposide (VP-16) and cisplatin in extensive stage small cell lung cancer (SCLC). Proc Am Soc Clin Oncol 10: 240
4. Loehrer PJ, Einhorn LH, Greco FA (1988) Cisplatin plus etoposide in small cell lung cancer. Semin Oncol 15: 2
5. Luikart SD, Propert KJ, Modeas CR, Green MR, Perry MC (1987) High-dose etoposide therapy for extensive small cell lung cancer: a Cancer and Leukemia Group B study. Cancer Treat Rep 71: 533
6. Miller AA, Stewart CF, Tolley EA (1990) Clinical pharmacodynamics of continuous-infusion etoposide. Cancer Chemother Pharmacol 25: 361
7. Ratain MJ, Schilsky RL, Conley BA, Egorin MJ (1990) Pharmacodynamics in cancer therapy. J Clin Oncol 8: 1739
8. Ratain MJ, Mick R, Schilsky RL, Vogelzang NJ, Berezin F (1991) Pharmacologically based dosing of etoposide: a means of safely increasing dose intensity. J Clin Oncol 9: 1480
9. Slevin ML, Clark PI, Joel SP, Malik S, Osborne RJ, Gregory WM, Lowe DG, Reznek RH, Wrigley PFM (1989) A randomized trial to evaluate the effect of schedule on the activity of etoposide in small-cell lung cancer. J Clin Oncol 7: 1333
10. Sokal RR, Rohlf FJ (1981) Single classification analysis of variance. In: Biometry: the principles and practice of statistics in biological research, 2nd edn. W. H. Freeman and Co., New York, p 208
11. Stewart CF, Arbuck SG, Fleming RA, Evans WE (1990) Changes in the clearance of total and unbound etoposide in patients with liver dysfunction. J Clin Oncol 8: 1874
12. Stewart CF, Arbuck SG, Fleming RA, Evans WE (1991) Relation of systemic exposure to unbound etoposide and hematologic toxicity. Clin Pharmacol Ther 50: 385