Cancer Chemother Pharmacol (1996) 39: 61–66

ORIGINAL ARTICLE

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Pharmacodynamic modeling of prolonged administration of etoposide

Received: 27 July 1995/Accepted: 18 March 1996

Abstract *Purpose*: A refined pharmacodynamic model for toxicity is necessary for successful adaptive control of the administration of an anticancer drug to avoid toxicity. We sought to establish a pharmacodynamic model of leukopenia in a 14-day administration of etoposide. *Methods*: Pharmacokinetic data of 32 patients treated with etoposide infused over 14 days in a phase I study (20 patients) or in an adaptive control study (12 patients) were used to develop a model for the prediction of a leukocyte nadir count. The concentrations of both estimated unbound and total etoposide at steady state, as well as patient demographic factors, were included in linear and nonlinear models. The unbound fraction of etoposide was estimated using an equation based on serum albumin and total bilirubin. The efficacy of the models was evaluated in terms of correlation coefficient (r), mean predictive error (MPE) and root mean square error (RMSE). *Results*: For both total and unbound drug concentration, a nonlinear model predicted leukopenia more precisely and with less bias than a linear model, and unbound drug explained more variability of leukopenia than total drug concentration in both linear and nonlinear models. The best model was a nonlinear model with three variables of unbound concentration, pretreatment leukocyte count and prior treatment ($r = 0.76$, MPE $\pm$ SEM $= 0.07 \pm 0.17 \times 10^3/\mu l$, RMSE $= 0.95 \times 10^3\ \mu l$), which was better than the best linear model. *Conclusions*: The nonlinear model using unbound etoposide concentration explained the interpatient variability of leukocyte nadir count to a fairly large extent. Although the model provided useful information on the pharmacodynamics of etoposide, it was still imprecise and a more refined model is necessary for application to an adaptive control study.

Key words Pharmacodynamics · Pharmacokinetics · Etoposide · Leukopenia · Cancer

Introduction

Etoposide is active against small-cell lung cancer, germ cell tumors, leukemia, and malignant lymphoma, and probably also against non-small-cell lung cancer [4, 13]. Preclinical and clinical observations suggested that prolonged exposure to etoposide should enhance its efficacy [3, 16, 18, 24] and clinical trials using oral administration for 14 or 21 days have been widely conducted [6, 7, 11, 12, 23]. In prolonged administration of etoposide, a relationship between the plasma concentration of the drug and leukopenia which is the dose-limiting toxicity has been suggested [9, 11]. However, it has large variability and needs to be refined before it is applied in an adaptive control trial with the intention of decreasing toxicity.

We have previously conducted two clinical studies of etoposide using a 14-day intravenous infusion. A phase I study indicated that there is a pharmacodynamic relationship between plasma concentration of etoposide and toxicity [10]. In the second study we measured the concentration of etoposide at 24 h after the initiation of chemotherapy and tried to avoid toxicity by

This work was supported in part by a grant from the Uehara Memorial Foundation, Japan, and by a Grant-in-Aid for Cancer Research (7–30) from the Ministry of Health and Welfare in Japan

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adjusting the infusion rate of the drug toward a target concentration of 1.5 μg/ml [2]. Although the plasma concentration was successfully controlled around 1.5 μg/ml, the frequency of severe toxicity was not decreased compared to the patients treated with the same range of doses in the previous phase I study. We felt that a refined pharmacodynamic model was necessary to avoid toxicity.

Etoposide has been reported to be highly bound to plasma proteins and wide interpatient variability of the unbound fraction of etoposide ranging from 5% to 50% has been observed in patients with cancer [19–21]. The unbound fraction of a drug in plasma generally correlates better with pharmacological effects than does the total drug because only unbound drug is available for membrane transport and interaction with receptors. In this study we used an equation reported by Stewart et al. to estimate the unbound fraction of etoposide based on serum albumin and total bilirubin [20], and we sought to establish a pharmacodynamic model using estimated unbound drug concentrations. Furthermore, wide interpatient variability of toxicity is usually observed even among patients with similar pharmacokinetic parameters. Characterizing the interpatient pharmacodynamic variability increases our understanding of patient factors which impact on the pharmacodynamics of a drug. We sought to increase the performance of pharmacodynamic models by including patient demographic factors.

Patients and methods

Data for this study were derived from 32 patients treated with etoposide infused over 14 days. Of these patients, 20 were treated in a phase I study in which the dose of each patient was fixed and ranged from 300 to 700 mg/m^2 per 14 days [10], and the remaining 12 patients received the drug in an adaptive control study. In these patients, the plasma etoposide concentration 24 h after the initiation of chemotherapy at a dose rate of 40 mg/m^2 per day was measured, and the infusion rate was adjusted within 6 h to achieve a target concentration of 1.5 μg/ml based on the assumption of linear pharmacokinetics of etoposide [2]. Actually, the dose rate was adjusted to 35 ± 6 mg/m^2 per day (mean ± SD) and the etoposide concentration was changed from 1.8 ± 0.4 μg/ml (mean ± SD) at 24 h to 1.6 ± 0.2 μg/ml after the dose adjustment. Etoposide was administered using a drip pump or a syringe pump through a central venous catheter. Etoposide solution was prepared every 12 h for the drip infusion, or the syringe containing undiluted etoposide was changed daily without interrupting the administration in any patient. All patients were treated as inpatients and completed the 14-day chemotherapy treatment, and blood cell counts were monitored two to six times a week depending on the toxicity.

In this study, only data from the first cycle were used for the development of a pharmacodynamic model for a leukocyte count at nadir (WBC_{nad}). We chose WBC_{nad} as a pharmacodynamic parameter instead of absolute neutrophil count because the data for the latter were incomplete in some patients. Detailed demographic and pharmacologic data of each study have been reported elsewhere [2, 10]. Between the two studies, there was no difference in total or unbound drug concentrations, coefficients of variation of concentration at steady-state in each patient, or WBC_{nad} (Table 1). At steady-state, six (24, 48, 120, 192, 264 and 336 h after the initiation of chemotherapy) and four (96, 192, 288 and 336 h) timed blood samples were obtained in the phase I study and the adaptive control study, respectively, and blood was drawn 192 h after the initiation of

Table 1 Demographic and pharmacokinetic data of patients. The presented values are range and mean ± standard deviation (*WBC* white blood cell count, C_{192} concentration 192 h after the initiation of chemotherapy, *mean concentration* arithmetic mean of concentrations in each patient at steady state, *CV* intrapatient coefficient variation)

	Phase I	Adaptive control	Total
Albumin (g/dl)	3.0–4.7 (4.0 ± 0.5)	3.1–4.7 (3.8 ± 0.6)	3.0–4.7 (3.9 ± 0.5)
Total bilirubin (mg/dl)	0.2–1.0 (0.5 ± 0.2)	0.3–1.5 (0.7 ± 0.4)	0.2–1.5 (0.6 ± 0.3)
Pretreatment WBC (/μl)	3500–19 500 (7700 ± 3500)	4900–11 100 (7600 ± 2100)	3500–19 500 7700 ± 3000)
Nadir WBC (/μl)	200–6300 (2800 ± 1700)	100–3800 (2500 ± 1100)	100–6300 (2700 ± 1500)
Unbound fraction	0.0087–0.13 (0.061 ± 0.034)	0.0146–0.1241 (0.071 ± 0.038)	0.0087–0.13 (0.065 ± 0.035)
C_{192} (μg/ml)	0.6–2.7 (1.6 ± 0.6)	1.3–2.3 (1.8 ± 0.3)	0.6–2.7 (1.6 ± 0.5)
Free C_{192} (μg/ml)	0.012–0.200 (0.091 ± 0.054)	0.022–0.223 (0.122 ± 0.062)	0.012–0.223 (0.102 ± 0.058)
Mean concentration (μg/ml)	0.8–2.9 (1.5 ± 0.6)	1.2–2.0 (1.6 ± 0.2)	0.8–2.9 (1.6 ± 0.5)
CV of mean concentration (%)	5–40 (15 ± 9)	5–25 (13 ± 7)	5–40 (14 ± 9)

chemotherapy in both studies. We used this concentration (C_{192}) for the development of a model, because the numbers of samples at steady-state were different in the two studies. When we compared the C_{192} and the mean concentration at steady-state in each patient, the correlation was very high ($r = 0.90$) which was expected from the modest intrapatient variability (14%).

Total plasma concentrations of etoposide were measured by high-pressure liquid chromatography [1] and the unbound drug concentrations were estimated by multiplying the total drug concentration by the unbound fraction (fu). For the estimation of fu, we used an equation which Stewart et al. developed using data from patients with hyperbilirubinemia [20]: $\text{fu} = 0.346 - 0.074 \times \text{serum albumin} + 0.015 \times \text{total bilirubin}$. Before using this equation in this study, we validated it with values for fu, serum albumin and total bilirubin, which were reported by the same authors in a separate publication [19]. We calculated fu using the above equation and the values of albumin and bilirubin in each patient with normal bilirubin levels. When we compared the calculated fu with the measured value, it was unbiased and precise: the mean prediction error (MPE) and root mean square error (RMSE) [17] were -5% and 28%, respectively. MPE and RMSE were calculated as: $\text{MPE} = 1/n\ \Sigma(\text{PRED} - \text{OBS})$, $\text{RMSE} = [1/n\ \Sigma(\text{PRED} - \text{OBS})^2]^{1/2}$ where PRED, OBS and n are the predicted value by the model, actually observed value and the number of the samples, respectively.

In the development of the pharmacodynamic model predicting WBC_{nad}, we used either linear or nonlinear models and the best model was selected based on the correlation coefficient, MPE and RMSE between observed and predicted WBC_{nad}. For the linear model, etoposide concentrations and the following demographic factors were included in the multiple linear regression: age (years), performance status (0, 1, 2), gender (male = 0, female = 1), prior treatment with chemotherapy and/or radiotherapy (no = 0, yes = 1), serum albumin (g/dl), total bilirubin (mg/dl), creatinine (mg/dl), leukocyte count (/ μl) before chemotherapy (WBC_{pre}), intrapatient coefficient of variation of the drug level at steady-state (%), and the type of treatment (phase I = 0, adaptive control = 1). WBC_{pre} and WBC_{nad} were log-transformed before incorporation into a model, and to avoid multicollinearity, covariates showing correlation ($r > 0.4$) with other covariates were excluded. All possible combinations of one, two, three, four and five variables were tested in multiregression, and the best linear models with one, two, three, four and five variables were selected based on the multiple correlation coefficient for $\ln WBC_{nad}$ and further evaluated by simple correlation coefficient, MPE and RMSE between observed and predicted WBC_{nad} (not $\ln WBC_{nad}$). Linear regressions were performed using NCSS 6.0 (Number Cruncher Statistical Systems, Kaysville, Utah).

For the nonlinear model, we began with a modified sigmoid inhibitory effect model (model 2 in Table 2) which contains two constants: concentration constant yielding half maximal effect (K) and sigmoid factor of the curve (n). Etoposide concentration, age, serum albumin, total bilirubin, prior treatment or performance status were tested as a variable in model 2, and as expected, unbound etoposide concentration gave the highest correlation between actual and model-predicted WBC_{nad}. We sought to refine model 2 with unbound concentration by including a patient demographic factor which showed the highest correlation with the residual of the model. In the inclusion of the second variable, we tested the impact of each factor on interaction with K, n or WBC_{pre} in models 3 to 8 listed in Table 2, and the best model was selected based on the correlation coefficient, MPE and RMSE. During the development of the nonlinear models, unweighted nonlinear fitting by the Nelder-Mead simplex algorithm was used in PCNONLIN (version 4.0, Scientific Consulting, Apex, N.C.).

Table 2 Pharmacodynamic models for leukocyte nadir counts. C and x in the models denote etoposide concentration and a demographic factor, respectively. Etoposide concentration was tested as x in models 1 and 2. α, β, n and K are constants

Model 1	$\ln WBC_{nad} = \alpha + \Sigma\beta_i x_i$
Model 2	$WBC_{nad} = WBC_{pre}\left(1 - \frac{x^n}{x^n + K^n}\right)$
Model 3	$WBC_{nad} = WBC_{pre}\left(1 - \frac{C^n}{C^n + (\alpha x + \beta)^n}\right)$
Model 4	$WBC_{nad} = WBC_{pre}\left(1 - \frac{C^{(\alpha x + \beta)}}{C^{(\alpha x + \beta)} + K^{(\alpha x + \beta)}}\right)$
Model 5	$WBC_{nad} = WBC_{pre}^{(\alpha x + \beta)}\left(1 - \frac{C^n}{C^n + K^n}\right)$
Model 6	$WBC_{nad} = WBC_{pre} - WBC_{pre}^{(\alpha x + \beta)}\left(\frac{C^n}{C^n + K^n}\right)$
Model 7	$WBC_{nad} = (\alpha x + \beta)\ WBC_{pre}\left(1 - \frac{C^n}{C^n + K^n}\right)$
Model 8	$WBC_{nad} = WBC_{pre} - (\alpha x + \beta)\ WBC_{pre}\left(\frac{C^n}{C^n + K^n}\right)$

Results

The coefficient of variation of the total concentration was 31%, and unbound concentration (57%) and WBC_{nad} (56%) had large interpatient variability (Table 1). When the number of variables in the linear model for $\ln WBC_{nad}$ was increased up to four by including unbound drug concentration, WBC_{pre}, prior treatment, and total bilirubin, RMSE was decreased from $1.37 \times 10^3/\mu l$ for the one-variable model to $1.10 \times 10^3/\mu l$ for the four-variable model. However, a five-variable model resulted in increased RMSE compared to the four-variable model (Table 3). Considering the decreased model performance and the risk of overfitting in the five-variable model, the four-variable model with unbound concentration was selected as the best linear model. Because this model included a categorical variable (prior treatment), we tried to make separate linear models for patients with or without prior treatment by using the covariates of unbound drug concentration, WPC_{pre} and total bilirubin. However, model performance in all patients combined was not improved ($r = 0.73$, $\text{MPE} \pm \text{SEM} = -0.17 \pm 0.21 \times 10^3/\mu l$, $\text{RMSE} = 1.18 \times 10^3/\mu l$). When we developed linear models with total etoposide concentration in the same way, the best model included C_{192}, $\ln WBC_{pre}$, albumin and prior treatment, but it was biased and imprecise (Table 3).

When the correlations of model 2 with each variable were evaluated, the unbound concentration showed the highest correlation (Table 4). Prior treatment had the highest correlation with the residual from model 2 with unbound concentration, and improved the model more than any other factor (Table 5). Because models 5 to 8 had equal or smaller correlations than model 4 with

Table 3 Performance for prediction of leukocyte nadir count (WBC_{nad}) of linear models with drug concentration: $\ln WBC_{nad} = \alpha + \Sigma\beta_i x_i$. *r* correlation coefficient between predicted and actual leukocyte nadir counts, *MPE* mean prediction error, *RMSE* root mean square error, *SE* (standard error of the regression coefficient) is the standard deviation of the estimate, $\ln WBC_{pre}$ log-transformed pretreatment white blood cell count, *PS* performance status

	Covariates					Coefficients						*r*	MPE ± SEM ($\times 10^3/\mu l$)	RMSE ($\times 10^3 \mu l$)
	x_1	x_2	x_3	x_4	x_5	α (SE)	β_1 (SE)	β_2 (SE)	β_3 (SE)	β_4 (SE)	β_5 (SE)			
1	Unbound C_{192}	–	–	–	–	8.2187 (0.2934)	− 5.624 (2.518)	–	–	–	–	0.44	− 0.45 ± 0.23	1.37
2	Unbound C_{192}	$\ln WBC_{pre}$	–	–	–	− 0.989 (3.477)	− 7.501 (2.403)	1.058 (0.398)	–	–	–	0.68	− 0.28 ± 0.20	1.16
3	Unbound C_{192}	$\ln WBC_{pre}$	Prior treatment	–	–	− 1.786 (3.364)	− 8.812 (2.410)	1.179 (0.388)	− 0.570 (0.305)	–	–	0.70	− 0.22 ± 0.20	1.14
4	Unbound C_{192}	$\ln WBC_{pre}$	Prior treatment	Bilirubin	–	− 0.257 (3.561)	− 9.124 (2.403)	1.045 (0.400)	− 0.560 (0.303)	− 0.549 (0.449)	–	0.74	− 0.20 ± 0.19	1.10
5	Unbound C_{192}	$\ln WBC_{pre}$	Prior treatment	Bilirubin	PS	− 0.6976 (3.596)	− 9.661 (2.471)	1.083 (0.402)	− 0.6068 (0.3071)	− 0.5746 (0.4505)	0.1588 (0.1657)	0.70	− 0.17 ± 0.21	1.20
6	Total C_{192}	$\ln WBC_{pre}$	Prior treatment	Albumin	–	− 3.524 (4.253)	− 0.777 (0.286)	1.024 (0.408)	− 0.627 (0.310)	0.891 (0.289)	–	0.70	− 0.27 ± 0.20	1.17

Table 4 Correlation coefficients between actual leukocyte nadir counts and predicted nadir counts by model 2 with each variable

	Unbound C_{192}	Total C_{192}	Bilirubin	Age	Albumin	Performance status	Prior treatment
Correlation coefficient	0.69	0.49	0.34	0.29	0.22	0.06	0.04

Table 5 Correlation coefficients between actual leukocyte nadir counts and predicted nadir counts by nonlinear models with two variables: unbound etoposide concentration and the second variable (*x*)

	Second variable (*x*)				
Model[a]	Prior treatment	Total bilirubin	Serum albumin	Age	Performance status
Model 3	0.73	0.69	0.69	0.69	0.71
Model 4	0.76	0.69	0.69	0.70	0.69
Model 5	0.71	0.69	0.69	0.69	0.70
Model 6	0.76	0.75	0.69	0.72	0.73
Model 7	0.71	0.71	0.69	0.70	0.70
Model 8	0.75	0.75	0.69	0.70	0.70

[a]Model numbers are the same as those in Table 2

prior treatment, and because models 5 to 8 had large standard errors of parameter estimation (more than 68%), we evaluated the MPE and RMSE of models 2 to 4 (Table 6). Even the simplest non linear model with unbound drug concentration and WBC_{pre} (model 2) demonstrated a high correlation with WBC_{nad}, and its MPE and RMSE (Table 6) was as good as the four-variable linear model (Table 3). Judging from the correlation coefficient, MPE and RMSE, model 4 with prior treatment as a covariate had the best model performance, although the absolute values of the residuals (mean ± SD) of model 2 ($0.92 \pm 0.59 \times 10^3/\mu l$) and model 4 ($0.82 \pm 0.45 \times 10^3/\mu l$) were not significantly different. Figure 1 is the scatter plot of observed leukopenia versus calculated leukopenia by this model, and Fig. 2 is the relationship between unbound drug concentraion and observed and calculated leukocyte nadir counts. We evaluated the correlation between the residuals of this model and other factors, but no factor showed a correlation greater than 0.16, nor improved the model when included.

Model 2 with total concentration showed a lower correlation and was more biased and imprecise than model 2 with unbound drug concentration (Table 6). Serum albumin correlated better with the residuals of model 2 with total drug concentration than any other

Table 6 Performance of nonlinear models with unbound etoposide concentration (α, β, *n* and *K* are the constants in the models listed in Table 2, *r* correlation coefficient between predicted and actual leukocyte nadir counts, *MPE* mean prediction error, *RMSE* root mean square error, *SE* standard error of the estimate)

Model	concentration	*x*	*n* (SE)	*K* (SE)	α (SE)	β (SE)	*r*	MPE ± SEM ($x10^3$/μl)	RMSE ($x10^3$/μl)
Model 2	Unbound	–	0.77 (0.19)	0.033 (0.008)	–	–	0.69	0.08 ± 0.19	1.09
Model 3	Unbound	Prior treatment	0.88 (0.17)	–	− 0.022 (0.006)	0.047 (0.004)	0.73	0.05 ± 0.19	1.00
Model 4	Unbound	Prior treatment	–	0.037 (0.004)	0.89 (0.20)	0.68 (0.12)	0.76	0.07 ± 0.17	0.95
Model 2	Total	–	0.56 (0.080)	0.37 (0.06)	–	–	0.49	0.22 ± 0.24	1.33
Model 3	Total	Albumin	0.87 (0.34)	–	0.56 (0.18)	− 1.52 (0.68)	0.68	0.21 ± 0.20	1.14
Model 4	Total	Albumin	–	0.69 (0.12)	3.24 (0.53)	0.38 (0.16)	0.65	0.16 ± 0.20	1.14

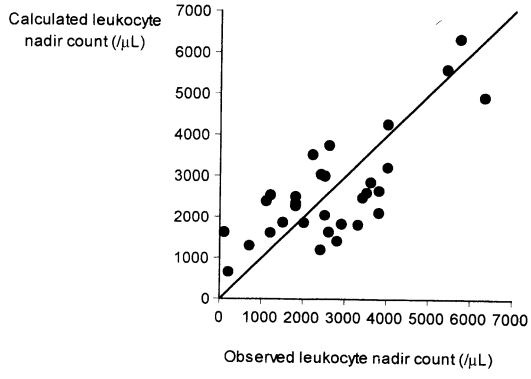

Fig. 1 Scatter plots of observed leukocyte nadir count versus leukocyte nadir count calculated by model 4 with prior treatment. Model 4 is defined by $WBC_{nad} = WBC_{pre}\ \{1 - C^{(0.89x+0.68)}/[C^{(0.89x+0.68)} + 0.037^{(0.89x+0.68)}]\}$ where $x = 0$ for patients without prior chemotherapy or radiotherapy and $x = 1$ for patients with prior chemotherapy and/or radiotherapy. The solid line represents the line of identity

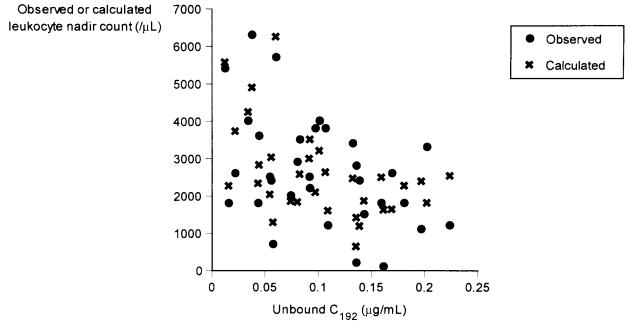

Fig. 2 Relationship between unbound etoposide concentration and observed and calculated leukocyte nadir count

factor, and again model 4 had a lower MPE than model 2 or 3 (Table 6). Although the bias and precision of model 4 was improved further (MPE ± SEM = 0.15 ± 0.18×10^3/μl, RMSE = 1.01×10^3/μl) by including total bilirubin and prior treatment into the sigmoid factor, it was more biased and imprecise than model 4 with unbound concentration and prior treatment. When we evaluated model 4 with unbound mean concentration at steady-state (not C_{192}) and prior treatment, model performance was not improved (MPE ± SEM = 0.08 ± 0.17×10^3/μl, RMSE = 0.96×10^3/μl).

Discussion

Stewart et al. developed two similar equations for the estimation of the unbound fraction of etoposide based on serum albumin and total bilirubin [19, 20]. Although they validated the first equation [19] using separate patients' data including patients with hyperbilirubinemia, it was biased (%MPE = 26%) and imprecise (%RMSE = 38%) in patients without hyperbilirubinemia [21]. Therefore we felt that it could not be used for our patients with normal bilirubin levels. When we validated the second equation [20] using data from the patients with normal bilirubin levels in their first study [19], the equation was unbiased and precise, although the reasons why similar equations gave different results and the exact role of bilirubin in the equation for patients with normal bilirubin levels were not clear, considering that in vitro displacement of etoposide from binding sites on albumin has been observed at 15 mg/dl of bilirubin [5]. Using the second equation, we estimated the unbound drug concentration in this study, and it correlated with leukopenia better than total drug concentration. Stewart et al. reported similar results in a conventional short-time infusion schedule by using area under the concentration versus time curve as a pharmacokinetic parameter [22]. The equation for the estimation of unbound fraction of etoposide is a robust method for pharmacodynamic evaluation of etoposide.

Even the simple nonlinear model with no patient demographic factor except for WBC_{pre} (model 2)

described the pharmacodynamic relationship as well as the best linear model with four patient demographic factors. This is in accordance with previous observations by Mick and Ratain for a 72-h infusion of etoposide [8]. We were able to refine the nonlinear model by including information on prior treatment, and the relationship between observed leukopenia and calculated leukopenia showed a good correlation. Ratain et al. conducted an adaptive control study of etoposide using a linear model in 72-h infusion schedule where the coefficient of variation of nadir counts was not decreased compared with that derived from a fixed dosing [15]. Although the nonlinear model with unbound concentration developed in this study could predict the nadir count fairly well judging from the scatter plots (Fig. 1) which seemed to be better than those using a 72-h infusion [8, 14], it explained only 58% of the variability in leukocyte nadir count. It had considerable variability, with an RMSE of about $1 \times 10^3/\mu l$, and was positively biased especially for patients with leukopenia less than $2 \times 10^3/\mu l$ (Fig. 1) for whom we need to precisely predict leukopenia. These observations preclude us from using this model in a future adaptive control study, but it gave us useful information on factors affecting leukopenia: unbound drug concentration and prior treatment. We used C_{192}, not mean concentration, as a representative concentration at steady-state for the development of models because the numbers of blood samples were different in the two studies and because the intrapatient variation of steady-state concentration was modest (14% as a coefficient of variation). When we developed models using the mean concentration instead of C_{192}, model performance was not improved. Although blood cell counts were monitored more often in some patients who had severe toxicities, most patients had blood counts twice weekly. If we had checked blood counts every day in all patients, the model would have been more accurate. However, such intensive monitoring is clinically impractical. The relationship between pharmacokinetics and pharmacodynamics of a drug is complicated by confounding factors such as interpatient variability in distribution to the target site or sensitivity to the drug. We may be able to refine the model by including information on these factors if available in future studies.

References

1. Allen LM (1980) Analysis of 4'-demethylepipodophyllotoxin-9-(4,6-O-ethilidene-β-D-glucopyranoside) by high-pressure liquid chromatography. J Pharm Sci 69:1440
2. Ando Y, Minami H, Sugiura S, Ando M, Nomura F, Sakai S, Saka H, Shimokata K (1996) Therapeutic drug monitoring of etoposide in a 14-day infusion for non-small-cell lung cancer. Jpn J Cancer Res 87:200
3. Dombernowsky P, Nissen NI (1973) Schedule dependency of the antileukemic activity of the podophyllotoxin-derivative VP 16–213 (NSC-141540) in L1210 leukemia. Acta Pathol Microbiol Scand [A] 81:715
4. Fleming RA, Miller AA, Stewart CF (1989) Etoposide: an update. Clin Pharm 8:274
5. Fleming RA, Evans WE, Arbuck SG, Stewart CF (1992) Factors affecting in vitro protein binding of etoposide in humans. J Pharm Sci 81:259
6. Hoskins PJ, Swenerton KD (1994) Oral etoposide is active against platinum-resistant epithelial ovarian cancer. J Clin Oncol 12:60
7. Johnson DH, Greco FA, Strupp J, Hande KR, Hainsworth JD (1990) Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. J Clin Oncol 8:1613
8. Mick R, Ratain MJ (1991) Modeling interpatient pharmacodynamic variability of etoposide. J Natl Cancer Inst 83:1560
9. Miller AA, Tolley EA, Niell HB, Griffin JP, Mauer AM (1993) Pharmacodynamics of prolonged oral etoposide in patients with advanced non-small-cell lung cancer. J Clin Oncol 11:1179
10. Minami H, Shimokata K, Saka H, Saito H, Ando Y, Senda K, Nomura F, Sakai S (1993) Phase I clinical and pharmacokinetic study of a 14-day infusion of etoposide in patients with lung cancer. J Clin Oncol 11:1602
11. Minami H, Ando Y, Sakai S, Shimokata K (1995) Clinical and pharmacologic analysis of hyperfractionated daily oral etoposide. J Clin Oncol 13:191
12. Murphy PB, Hainsworth JD, Greco FA, Hande KR, DeVore RF, Johnson DH (1992) A phase II trial of cisplatin and prolonged administration of oral etoposide in extensive-stage small cell lung cancer. Cancer 69:370
13. Radice PA, Bunn PA Jr, Ihde DC (1979) Therapeutic trials with VP-16–213 and VM-26: active agents in small cell lung cancer, non-Hodgkins lymphomas, and other malignancies. Cancer Treat Rep 63:1231
14. Ratain MJ, Schilsky RL, Choi KE, Guarnieri C, Grimmer D, Vogelzang NJ, Senekjian E, Liebner MA (1989) Adaptive control of etoposide administration: impact of interpatient pharmacodynamic variability. Clin Pharmacol Ther 45:226
15. 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
16. Roed H, Vindelov LL, Christensen IJ, Spang-Thomsen M, Hansen HH (1987) The effect of the two epipodophyllotoxin derivatives etoposide (VP-16) and teniposide (VM-26) on cell lines established from patients with small cell lung carcinoma of the lung. Cancer Chemother Pharmacol 19:16
17. Sheiner LB, Beal SL (1981) Some suggestions for measuring predictive performance. J Pharmacokinet Biopharm 9:503
18. 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
19. Stewart CF, Pieper JA, Arbuck SG, Evans WE (1989) Altered protein binding of etoposide in patients with cancer. Clin Pharmacol Ther 45:49
20. 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
21. Stewart CF, Fleming RA, Arbuck SG, Evans WE (1990) Prospective evaluation of a model for predicting etoposide plasma protein binding in cancer patients. Cancer Res 50:6854
22. Stewart CF, Arbuck SG, Fleming RA, Evans WE (1991) Relation of systemic exposure to unbound etoposide and hematologic toxicity. Clin Pharmacol Ther 50:385
23. Waits TM, Johnson DH, Hainsworth JD, Hande KR, Thomas M, Greco FA (1992) Prolonged administration of oral etoposide in non-small-cell lung cancer: a phase II trial. J Clin Oncol 10:292
24. Wolff SN, Grosh WW, Prater K, Hande KR (1987) In vitro pharmacodynamic evaluation of VP-16–213 and implications for chemotherapy. Cancer Chemother Pharmacol 19:246