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Boon C. Goh · Gini F. Fleming · Linda Janisch
Nicholas J. Vogelzang · Walter M. Stadler
Mark J. Ratain

Development of a schedule-dependent population pharmacodynamic model for rhizoxin without quantitation of plasma concentrations

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Abstract In previous phase I reports of short bolus infusion of rhizoxin, problems in assay sensitivity prevented the description of pharmacokinetic-pharmacodynamic relationships, and a pharmacologically guided approach to dose escalation was deemed not feasible. In this report, we describe a mathematical model, which explains the schedule-dependent interpatient pharmacodynamic variability of rhizoxin administered on a continuous infusion schedule. Using patient demographic and toxicity data from 45 patients treated in a phase I dose and duration escalation study of rhizoxin, we sought to model the nadir neutrophil count. We hypothesized that a surrogate derived variable based on dose and duration would reflect a pharmacokinetic parameter that would be a significant covariate. Multiple linear regression analysis was carried out to determine the other significant covariates. Dose/m^2 × LogDUR/ALB was significantly correlated with the $\text{LogANC}_{\text{nadir}}$ (Log_{10} neutrophil nadir; $r = 0.56$, $P < 0.001$). Other significant covariates included baseline performance status (PS), baseline serum bilirubin (BIL), and Log_{10} baseline neutrophil count ($\text{LogANC}_{\text{baseline}}$). Model bias and precision were assessed using the mean prediction error (MPE) and the root mean square error (RMSE) of the $\text{ANC}_{\text{nadir}}$, respectively. We constructed 1–4 covariate models. The variability of $\text{ANC}_{\text{nadir}}$ was modeled with good precision and accuracy with a 4-covariate model (MPE and RMSE $0.113 \pm 0.182 \times 10^3$ cells/μl and 1.22×10^3 cells/μl, respectively). This model should be validated and improved on with further clinical data. We believe that such pharmacodynamic modeling should be explored further to determine its performance and clinical relevance compared with modeling using pharmacokinetic parameters.

Key words Rhizoxin · Continuous infusion · Pharmacodynamic model

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B. C. Goh · G. F. Fleming (✉) · L. Janisch · N. J. Vogelzang
W. M. Stadler · M. J. Ratain
University of Chicago, Section of Hematology/Oncology,
5841 S. Maryland Avenue, MC 2115, Chicago,
IL 60637-1470, USA
e-mail:gfflemin@mcis.bsd.uchicago.edu
Tel.: +1-773-7026712; Fax: +1-773-7020963

G. F. Fleming · N. J. Vogelzang · W. M. Stadler · M. J. Ratain
Cancer Research Center,
University of Chicago, Chicago, Illinois, USA

M. J. Ratain
Committee on Clinical Pharmacology,
University of Chicago, Chicago, Illinois, USA

Introduction

The rationale of studying pharmacodynamic relationships in anticancer agents is to allow better understanding of interpatient variability of effect measures, and in this way enhance the development of the agent or improve its clinical use [1, 2]. Pharmacodynamic modeling allows a quantification of these relationships, and prediction of clinical endpoints based on pharmacokinetic and patient demographic variables. Much work in population pharmacokinetic/pharmacodynamic modeling has concentrated on pharmacokinetic parameters such as area under the concentration-time curve (AUC), peak plasma drug concentration, time above a certain plasma drug concentration, and concentration at steady state (for continuous infusions). However since pharmacokinetic parameters are often correlated with patient demographic variables, we hypothesized that a population pharmacodynamic model could be developed without actually measuring plasma concentrations. Given the technical difficulties of such measurements, the use of models based entirely on common clinical variables may result in a more applicable model. Although pharmacodynamic models have been developed for many anticancer drugs, it has been difficult to develop models that

may be applicable to different treatment schedules. Such models have been successfully developed for both etoposide and paclitaxel [3, 4, 5, 6, 7, 8, 9].

Rhizoxin, another antimitotic agent, is a macrocyclic lactone derived from *Rhizopus chinesis*, a plant pathogenic fungus that causes rice seedling blight [10]. It exerts cytotoxicity by inhibition of microtubule assembly and causes cell cycle arrest in the G2-M phase [11]. In previous pharmacokinetic studies of short bolus infusions, the drug has been difficult to assay at the lower concentrations. Limited pharmacokinetic data have revealed rapid clearance and short half-life [12, 13].

Because of the evident schedule-dependent cytotoxicity and the apparently short half-life, a phase I study of rhizoxin was conducted by continuous infusion to try to improve its therapeutic index. Based on the clinical data from this phase I study (3- to 72-h continuous infusion), we developed a pharmacodynamic model which explains the interpatient variability in the nadir neutrophil count.

Methods

Eligibility criteria included histologically confirmed solid tumor or lymphoma refractory to standard therapy or for which no effective therapy exists, Karnofsky performance status $\geq 60\%$, age ≥ 18 years, measurable disease, satisfactory hematological (baseline neutrophil count $\geq 2{,}000/\mu l$, leukocyte count $\geq 4{,}000/\mu l$, platelet count $\geq 100{,}000/\mu l$), renal (serum creatinine ≤ 1.6 mg/dl or creatinine clearance ≥ 50 ml/min), and hepatic (total bilirubin ≤ 1.5 mg/dl, aspartate transaminase $\leq 3 \times$ the upper limit of normal) functions. All patients gave written informed consent according to Federal and institutional guidelines. Rhizoxin is poorly water-soluble and has a tendency to precipitate in saline and dextrose solutions. In addition, the drug undergoes both thermal and photo decomposition at room temperature, with less than 10% loss for 12 h when diluted with a 10% lipid solution. Therefore, to minimize drug decomposition, patients in this study received rhizoxin reconstituted in 10% parenteral lipid solution in 100-ml bags and infused at a constant rate through a central venous catheter. For infusions of 24 h and longer, the dose was divided into 8-h bags, each of which was mixed within 4 h of initiating rhizoxin infusion. Special care was taken to avoid any interruption in dosing with each new infusion bag. The starting dose of rhizoxin was 1 mg/m^2, which was considered clinically safe because it represents 50% of the recommended phase II dose given as a bolus infusion every 3 weeks. This dose was given in increasing duration of infusion from 3 h, 8 h, 24 h, 48 h, and 72 h. Non-hematological dose-limiting toxicity (DLT) was defined as any grade 3 or 4 non-hematological toxicity other than nausea, vomiting or fatigue. Hematological DLT was defined as thrombocytopenia less than $20000/\mu l$, grade 4 neutropenia for more than 3 days or neutropenic fever. No intrapatient dose escalations were allowed. A minimum of three patients was treated at each dose level. The third patient entered at a given dose level was observed for at least 3 weeks prior to enrolling the first patient at the next dose level. If DLT was observed in any of the first three patients at a dose level, up to six patients were treated at that dose. The maximum tolerated dose (MTD) was, for the purposes of this trial, equivalent to the recommended phase II dose, and was defined as the dose level below that which resulted in DLT in two or more of six patients.

As dose-limiting neutropenia was reached at 48 h, the dose was reduced to 0.6 mg/m^2 and the duration of infusion increased from 48 h to 72 h. The dose was further escalated until the MTD was reached. Patient assessment included baseline history, physical examination, complete blood count (CBC), serum chemistries, electrocardiogram, chest x-ray, and tumor measurements. During treatment, patients had twice weekly CBCs (separated by at least 3 days) for the first two cycles and weekly CBCs for subsequent cycles. If grade 3 or greater hematological toxicity was noted in a patient, a CBC was performed three times a week until the toxicity resolved. Weekly physical examination and serum chemistries were also done. Tumor assessments were performed every two cycles of treatment.

Pharmacodynamic modeling

Our previous work has suggested that logarithm transformation of the nadir neutrophil value may be an appropriate dependent variable for purposes of exploring pharmacodynamic relationships. This is based on logarithmic transformation of the equation: $SF = e^{[-kC]}$, which yields a linear relationship Ln (nadir value) = Ln (pretreatment value) – kC, where SF is the survival fraction of cells and k is the rate constant that determines the slope of the decay curve, C is the plasma concentration of the anti-neoplastic agent under study, and Ln is the natural logarithm [3, 22]. In addition, logarithmic transformations of the predictor variables used in the modeling often allow better fitting of the data through stabilization of their variances. The reason for this lies in the possible existence of polynomial relationships (powers of the predictor variables) between the predictor variables and the dependent variable, which in the case of anti-neoplastic agents given in continuous infusion over varying duration of exposure, has theoretical basis (see Discussion). For the above reasons, logarithm transformations of both dependent and predictor variables were utilized in the analyses in this study. Only full data sets obtained from the first cycle of treatment were used in the mathematical modeling of the ANC_{nadir}. Descriptive statistics were first applied to determine the variability of ANC_{nadir} in the patient data set. The effect of an anticancer drug is generally dependent on both concentration and duration of exposure. Depending on the schedule dependence of the drug, the effect may be more dependent on either concentration, or exposure time [14, 15]. Therefore we assigned a pharmacokinetic parameter, γ, which would be significantly correlated with ANC_{nadir}; γ could represent the AUC or time above a threshold concentration. These parameters are measures of "drug exposure", and have been shown to be significant pharmacokinetic parameters in models predicting toxicity from anticancer agents. Pharmacologically, γ would be related to the dose and the duration of infusion, and we hypothesized that a surrogate variable based on dose/m^2 and duration of infusion would be an appropriate substitute for γ and would be significantly correlated with ANC_{nadir}. Serum albumin (g/dl), a reflection of the synthetic hepatic function which often correlates with clearance [16, 17], was included in this primary covariate. Log transformations of the duration of infusion and the dose were explored to fit the data to improve the correlation with Log_{10} neutrophil nadir ($LogANC_{nadir}$). Various derivations were studied including Dose/m^2 × LogDUR(Log_{10} duration of infusion)/ALB, Actual dose × Log DUR/ALB, Dose/m^2 × LogLogDUR/ALB, and the best correlated was selected to represent γ. Then using stepwise regression, covariates were selected based on their individual contributions to explaining the variability of Log ANC_{nadir}. All covariates (Table 3) including γ were included in the analysis. These included age (years), sex (male = 1, female = 2), race, performance status (using Karnofsky performance status), weight (kg), height (m), number of prior chemotherapy regimens, baseline total bilirubin (mg/dl), aspartate and alanine transaminases (U/l), total protein (g/dl), calculated creatinine clearance (ml/min), and Log_{10} baseline neutrophil count ($LogANC_{baseline}$). One variable was added at a time, and the regression and residual sum of squares was calculated, and the F statistic of the predictor model was then calculated as the ratio of the regression mean square to the residual mean square with the addition of the variable. The *P* value representing the probability of getting a larger value of the F statistic at a numerator degree of freedom of 1 and a denominator degree of freedom of *n*-k-2 was set at 0.05 (where *n* is the number of data sets studied and k is the number of covariates in the model). Therefore the null hypothesis of the coefficient of the

variable $\beta = 0$ was rejected and the new variable was entered if the calculated P value was less than 0.05 [18, 19, 20]. The variables were then added according to this criterion till it was determined that the remaining variables would not add any significant improvement to the model. At each step of the variable selection, the variables in the equation were tested for correlation with effect, and variables that had a P value greater than 0.01 were excluded from the model.

Using this stepwise method of variable selection, a 4-covariate model was constructed. The best single, 2- and 3-covariate models were determined as well. The coefficient of determination of each best model was calculated, and the models were tested for model bias and precision by calculating the mean predictive error (MPE) and the root mean square error (RMSE) of the observed and predicted $ANC_{nadir,}$ respectively [21]. Bivariate scatter plots of standardized residuals by the significant explanatory variables were studied to check the assumptions of linearity between the $LogANC_{nadir}$ and these variables and the lack of correlation of standardized residuals with each explanatory variable [22]. All significant covariates in the models developed were checked for collinearity using an analysis of the variance inflation factor; a variance inflation factor greater than 10 was indicative of collinearity. For the final 4-covariate model selected, analysis was repeated using forward regression and backward regression methods to assess consistency. All linear regressions were performed using the SPSS Version 7.5 (SPSS Incorporated, Chicago, Ill., USA) The best model was then utilized to predict the cycle 2 ANC_{nadir} of patients who received at least two cycles of rhizoxin and had full data sets for the second cycle.

Results

Forty-eight patients were accrued in the study, and 45 full data sets for the first treatment cycle were available for analysis. Patient characteristics are shown in Table 1. Hematological toxicity is summarized in Table 2. Neutropenia was the main DLT encountered, and the ANC_{nadir} had significant interpatient variability (coefficient of variation 74%). At the MTD of 0.8 mg/m^2 over 72 h, the ANC_{nadir} showed a coefficient of variation of 51%. Table 3 shows the results of univariate correlation of the covariates studied with the Log ANC_{nadir}. The best covariate representing γ was derived from the dose, duration of infusion and the serum albumin ($Dose/m^2 \times LogDUR/ALB$), which yielded a correlation coefficient (r) of 0.56 (P value < 0.001) in univariate analysis. Actual dose (without normalization to body surface area) was also studied in these derivations but did not result in a better correlation with $LogANC_{nadir}$. In the multiple regression analysis, three other covariates reached significance to merit inclusion in the model. These were the performance status (PS), the pretreatment total bilirubin (BIL), and the $LogANC_{baseline}$. However, the extent of overall variability explained by the addition of these other covariates were minor compared with the first covariate. Table 4 shows the four models developed, with their coefficients, correlation coefficients, MPE and RMSE. The addition of demographic variables improved the overall r from 0.56 to

Table 1 Patient characteristics

Number of patients	48
Sex	
Male	22
Female	26
Performance status	
0	28
1	18
2	2
Age (years)	
Median	58
Range	24–80
Prior radiotherapy	16
Number of prior chemotherapy regiments	
Median	2
Range	0–7
Tumor type	
Ovarian	8
Non-small cell lung cancer	8
Colorectal	8
Renal	5
Unknown primary	4
Squamous cell skin	3
Soft tissue sarcoma	2
Gastric	2
Pancreatic	2
Cholangiocarcinoma	2
Mesothelioma	1
Prostate	1
Thyroid	1
Breast	1

Table 2 Hematological toxicity (first cycle). *ANC*, *PLT*

Total rhizoxin dose (mg/m^2)	Infusion duration (h)	Infusion rate ($mg/m^2 \cdot h$)	Number of patients	Toxicity (grade)					
				ANC			PLT		
				2	**3**	**4**	**2**	**3**	**4**
1	3	0.333	3	1	0	0	0	0	0
1	8	0.125	8	0	0	0	0	0	0
1	24	0.042	9	1	1	0	0	0	0
1	48	0.021	4	0	2	1	0	0	0
0.6	48	0.013	6	0	1	1	0	0	0
0.6	72	0.008	3	2	0	0	0	0	0
0.8	72	0.011	16	3	1	0	0	1	0
1	72	0.014	4	0	1	2	0	0	0

ANC absolute neutrophil count
PLT platelet count

Table 3 Univariate linear regression of covariates tested with the $LogANC_{nadir.}$ *BIL* pretreatment total bilirubin, *BSA* body surface area, *PS* performance status

Covariates	r	r^2	β	SE (β)	Significance (P value)	F
Age	0.2	0.04	-9.08×10^{-3}	0.01	0.18	1.83
Sex	0.04	0.00	-4.05×10^{-2}	0.16	0.80	0.06
ALT	0.2	0.04	-4.14×10^{-3}	0.00	0.19	1.75
AST	0.04	0.00	-7.91×10^{-4}	0.00	0.78	0.08
BIL	0.18	0.03	−0.39	0.31	0.22	1.56
BSA	0.15	0.02	0.25	0.24	0.30	1.08
CrCl	0.26	0.07	3.1×10^{-3}	0.00	0.08	3.22
LogANCbaseline	0.04	0.00	0.12	0.43	0.79	0.07
PS	0.01	0.00	-3.75×10^{-4}	0.01	0.96	0.00
Race	0.01	0.00	4.4×10^{-3}	0.11	0.97	0.00
Total protein	0.15	0.02	0.11	0.11	0.33	0.97
Weight	0.11	0.01	2.16×10^{-3}	0.00	0.45	0.59
Number of prior chemotherapy regimens	0.08	0.01	-4.56×10^{-2}	0.01	0.61	0.26
Dose/ALB*LogDUR	0.50	0.25	−2.043	0.53	< 0.001	14.65
Actual Dose/ALB*LogDUR	0.39	0.16	−0.84	0.29	0.006	8.28
Dose/ALB*LogLogDUR	0.34	0.12	−4.60	1.89	0.019	5.95

0.74. Model bias was improved, with a reduction of the mean prediction error from 358 cells/μl in the 1-covariate model to 113 cells/μl in the 4-covariate model. Forward and backward multiple linear regression analysis gave consistent covariates and correlations. Visual inspection of the bivariate scatter plots of the standardized residuals by $LogANC_{nadir}$ showed means equal zero, constant variances, fulfilling the assumption of linearity. The final model was defined as:

$$\begin{aligned} \mathrm{LogANC_{nadir}} = & 2.603 - 2.969 * \mathrm{Dose/m^2/ALB} * \mathrm{LogDUR} \\ & - 0.0193 * \mathrm{PS} - 0.617 * \mathrm{BIL} \\ & + 0.781 * \mathrm{LogANC_{base}} \end{aligned}$$

Fig. 1 shows the scatter plot of the observed ANC_{nadir} against the corresponding predicted ANC_{nadir} values according to Model 4. The variance inflation factors for γ, PS, BIL, and LogANCnadir were 1.29, 1.32, 1.15, and 1.26, respectively, thus suggesting no significant collinearity between these covariates. The model was used to predict the ANC_{nadir} for cycle 2 in those patients who received two or more cycles of rhizoxin treatment. This set of data, comprising 35 complete data sets of patient dose, duration of infusion, prior treatment baseline performance status, serum total bilirubin, absolute neutrophil count, and albumin was used as the validation set. The 4-covariate model performed well as shown in Fig. 2 which shows the residuals (predicted ANC_{nadir} value – observed ANC_{nadir} value) of prediction for ANC_{nadir} for the second cycle of rhizoxin treatment. The ANC_{nadir} was well predicted by the model, with an RMSE of 0.92×10^3 cells/μl, and was unbiased (MPE $-0.06 \pm 0.16 \times 10^3$ cells/μl).

Other clinical data

The maximum tolerated dose in this study was 0.8 mg/m^2 over 72 h, with neutropenia being the DLT. Non-hematological toxicity was mild; only one patient experienced grade 3 mucositis at a dose of 1 mg/m^2 over 72 h. No responses were observed in this study.

Discussion

We believe this is the first report of the development of a population pharmacodynamic model for an anticancer drug, which relies entirely on dose, schedule, and patient demographics. The model was assessed for precision and bias using the RMSE and MPE, respectively, and performed well. This model is based on pharmacological principles; replacement of a pharmacokinetic parameter with a surrogate covariate based on dose and duration of infusion. Using the covariate Dose/m^2 × LogDUR/ALB, a significant correlation with the $LogANC_{nadir}$ was found. This is not surprising, considering that with continuous infusion schedules, the drug effect is a function of the concentration and the duration of infusion. The contribution of serum albumin in the equation suggests it may be a surrogate marker of clearance of rhizoxin. Interestingly, serum albumin was found to be a significant covariate to explain the marked variability of pharmacokinetics of vinblastine, another antimicrotubule agent [23, 24]. The 4-covariate model performed well in predicting the second cycle ANC_{nadir} of patients using second cycle data sets. However, this is not surprising, given that intrapatient pharmacodynamic variability is less than interpatient variability.

In vitro cell line pharmacodynamic models have been used to study the relationship between cytotoxicity represented by cell SF as a function of concentration (C) and exposure time (T) [25, 26, 27, 28, 29]. For some drugs, such as doxorubicin and cisplatin, the SF was found to be a simple function of C × T [26, 27]. However, for other drugs, such as methotrexate, the relationship was more complex. In general, the SF was found to be a power function of C and an exponential

Table 4 Performance for prediction of absolute neutrophil nadir count (ANC_{nadir}) of linear models: $LogANC_{nadir} = \alpha + \Sigma(\beta_i \chi_i)$; *r* correlation coefficient between predicted and actual ANC_{nadir}, *MPE* mean prediction error, *RMSE* root mean square error, *SE* standard error of the estimate, *Bil* serum bilirubin, *PS* performance status

Model	Covariates (*P* values)				Coefficients						
	χ_1	χ_2	χ_3	χ_4	α (SE)	β_1 (SE)	β_2 (SE)	β_3 (SE)	β_4 (SE)	*r*	MPE (cells/μl) (SE)	RMSE (cells/μl)
1	LogDUR*Dose/ALB (<0.001)				0.85 (0.20)	−2.19 (0.50)				0.56	−358.1 (191.4)	1312
2	LogDUR*Dose/ALB (<0.001)	PS (0.013)			2.44 (0.64)	−2.62 (0.50)	−1.70E−02 (0.006)			0.64	−193.5 (208.1)	1426.6
3	LogDUR*Dose/ALB (0.001)	PS (0.001)	Bil (0.017)		3.23 (0.70)	−2.59 (0.47)	−2.22E−02 (0.01)	−0.62 (0.25)		0.70	−165.7 (222.4)	1524.9
4	LogDUR*Dose/ALB (<0.001)	PS (0.004)	Bil (0.012)	LogANCbase (0.029)	2.60 (0.70)	−2.97 (0.48)	−0.02 (0.01)	−0.62 (0.24)	0.78 (0.34)	0.74	−113 (182)	1220

Fig. 1 Scatter plot of observed neutrophil nadir count versus neutrophil nadir count calculated by Model 4. The solid line is the line of identity

Fig. 2 Predicted ANC_{nadir} based on Model 4 versus observed ANC_{nadir} for cycle 2. ($n = 35$). The solid line is the line of identity

function of T. For example, Eichholtz and Trott [25] used a Chinese Hamster fibroblast model to demonstrate that $SF = 1.5 \times e^{-0.1\,T} \times C^{-0.15-0.02T}$. Keefe [28] used a murine leukemia cell line model to show that the best pharmacodynamic relationship based on a linear regression analysis was: $\text{Log SF} = 2.25 - 1.76 \times \text{Log T} - 0.31 \times \text{Log C}$. In our models we found that the $\text{Log}(ANC_{nadir}/ANC_{baseline})$, representing Log SF, was a function of the LogDUR multiplied by the Dose/m^2/ALB. There is therefore some mathematical similarity of our models to these models that supports the finding that the effect of cytotoxics is a complex function of concentration (or dose) and the duration of exposure. This finding has significance in modeling anticancer drugs given by varying lengths of infusion. To understand these relationships more clearly, based on our models, we omit the effect of PS and BIL, and derive $\text{Ln SF} = -k(\text{Dose/ALB}) \times \text{Ln T}$. Taking the antilogarithm,

yields $SF = e^{-k(Dose/ALB) \times Ln\ T} = e^{-k'(C) \times Ln\ T}$, considering the Dose/ALB represents a function of C. With this model, SF becomes one when $T = 1$, and therefore this cannot be a general model. Further studies of this nature with other drugs may elucidate a more general model of the complex relationship between dose, duration of infusion, and the pharmacodynamic effect.

It was interesting, if not surprising, to note the fairly high correlation coefficient, the low bias, and good precision of the model developed. As multiple linear regression analysis requires several assumptions to be fulfilled, standardized residuals were studied at each step of the analysis, and collinear covariates were excluded from the model to ensure these assumptions were not violated. Obviously validation of this model is needed using prospectively collected data before it can be applied clinically. However, as the mathematical procedures are relatively accessible with current computing capabilities, it should not be difficult to improve the model performance with iterative regression using additional data. Nonetheless, the model as described does fulfill the principal aim of a pharmacodynamic analysis, which is to identify and attempt to quantitate pharmacodynamic relationships.

Based on this study, we suggest that this approach may be investigated in other drugs, to determine whether there is consistency of modeling with and without pharmacokinetic data in the models developed. However, we realize that this study is based on varying duration of infusion and dose, which is not the conventional design of a phase I study of anti-neoplastic agents. Bearing this limitation in mind, if the approach is validated, it will represent an important research strategy in pharmacodynamic modeling, which may reduce the need for very laborious blood sampling requiring considerable logistics and patient discomfort, and may even find utility in routine practice. For drugs that are very difficult to assay because of problems of sensitivity, especially when administered by continuous infusion, this approach may offer a reasonable way to predict the toxicity of treatment based on easily determined parameters.

References

1. Ratain MJ, Schilsky RL, Conley BA, Egorin MJ (1990) Pharmacodynamics in cancer therapy. J Clin Oncol 8: 1739
2. Peck CC, Barr WH, Benet LZ, Collins J, Desjardins RE, Furst DE, Harter JG, Levy G, Ludden T, Rodman JH, Sanathanan L, Schentag JJ, Shah VP, Sheiner LB, Skelly JP, Stanski DR, Temple RJ, Viswanathan CT, Weissinger J, Yacobi A (1992) Opportunities for integration of pharmacokinetics, pharmacodynamics and toxicokinetics in rational drug development. Clin Pharmacol Ther 51: 465
3. Mick R, Ratain MJ (1991) Modeling interpatient pharmacodynamic variability of etoposide. J Natl Cancer Inst 83: 1560
4. Minami H, Ratain MJ, Ando Y, Shimokata K (1996) Pharmacodynamic modeling of prolonged administration of etoposide. Cancer Chemother Pharmacol 39: 61
5. Minami H, Sasaki Y, Saijo N, Ohtsu T, Fujii H, Igaarashi T, Itoh K (1998) Indirect-response model for the time course of leukopenia with anticancer drugs. Clin Pharmacol Ther 64: 511
6. Gianni L, Kearns CM, Giani A, Capri G, Vigano L, Locatelli A, Bonnadonna G, Egorin MJ (1995) Nonlinear pharmacokinetics and metabolism of paclitaxel and its pharmacokinetic/pharmacodynamic relationships in humans. J Clin Oncol 13: 180
7. Rowinsky EK (1997) Paclitaxel pharmacology and other tumor types. Semin Oncol 24 [Suppl 19]: S19-1–S19-12
8. Ohtsu T, Sasaki Y, Tamura T, Miyata Y, Nakanomyo H, Nishiwaki Y, Saijo N (1995) Clinical pharmacokinetics and pharmacodynamics of paclitaxel: a 3-hour infusion versus a 24-hour infusion. Clin Cancer Res 1: 599
9. Karlsson MO, Molnar V, Bergh J, Freijs A, Larsson R (1998) A general model for time-dissociated pharmacokinetic-pharmacodynamic relationship exemplified by paclitaxel myelosuppression. Clin Pharmacol Ther, 63: 11
10. Iwasaki S, Kobayashi H, Furukawa J, Namikoshi M, Ouda S, Sato Z, Matsuda I, Noda T (1994) Studies on macrocyclic lactone antibiotics. VII. Structure of a phytotoxin rhizoxin produced by *Rhizopus chinesis*. J Antibiot (Tokyo) 37: 354
11. Takahashi M, Iwasaki S, Kobayashi H, Okuda S, Murai T, Sato Y (1987) Rhizoxin binding to tubulin at the maytansine-binding site. Biochem Biophys Acta 962: 215
12. Hendriks HR, Plowman J, Berger DP, Paull KD, Fiebig HH, Fodstad O, Dreef-van der Meulen HC, Henrar REC, Pinedo HM, Schwartzmann G (1992) Preclinical antitumor activity and animal toxicology studies of rhizoxin, a novel tubulin-interacting agent. Ann Oncol 3: 755
13. Bissett D, Graham MA, Setanoians A, Chadwick GA, Wilson P, Koier I, Henrar R, Schwartzmann G, Cassidy J, Kaye SB, Kerr DJ (1992) Phase I and pharmacokinetic study of rhizoxin. Cancer Res 52: 2894
14. Vogelzang NJ (1984) Continuous infusion chemotherapy: a critical review. J Clin Oncol 2: 1289
15. Powis G (1985) Anticancer drug pharmacodynamics. Cancer Chemother Pharmacol 14: 177
16. McLean AJ, Morgan DJ (1991) Clinical pharmacokinetics in patients with liver disease. Clin Pharmacokinet 21: 42
17. Rowland M, Tozer TN (1995) Clinical pharmacokinetics: concepts and applications. Williams Wilkins, Philadelphia
18. Draper H, Smith H (1981) Applied regression analysis. Wiley, New York
19. Hocking RR (1976) Analysis and selection of variables in linear regression. Biometrics 32: 1
20. Neter J, Wasserman W, Kutner MH (1989) Applied linear statistical models. Irwin, Homewood, Illinois
21. Sheiner LB, Beal SL (1981) Some suggestions for measuring predictive performance. J Pharmacokinet Biopharm 4: 503
22. Mick R, Ratain MJ (1993) Statistical approaches to pharmacodynamic modeling: motivations, methods, and misperceptions. Cancer Chemother Pharmacol 33: 1
23. Ratain MJ, Vogelzang NJ, Sinkule JA (1987) Interpatient and intrapatient variability in vinblastine pharmacokinetics. Clin Pharmacol Ther 41: 61
24. Ratain MJ, Vogelzang NJ (1986) Phase I and pharmacological study of vinblastine by prolonged continuous infusion. Cancer Res 46: 4827
25. Eichholtz H, Trott KR (1980) Effect of methotrexate concentration and exposure time on mammalian cell survival in vitro. Br J Cancer 41: 277
26. Eichholtz-Wirth H, Hietel B (1986) The relationship between cisplatin sensitivity and drug uptake into mammalian cells in vitro. Br J Cancer 54: 239
27. Eichholtz-Wirth H (1980) Dependence of the cytostatic effect of Adriamycin on drug concentration and exposure time in vitro. Br J Cancer 41: 886
28. Keefe DA, Capizzi RL, Rudnick SA (1982) Methotrexate cytotoxicity for L5178Y/Asn-lymphoblasts: relationship of dose and duration of exposure to tumor cell viability. Cancer Res 42: 1641
29. Wilkoff LJ, Wilcox WS, Burdeshaw JA, Dixon GJ, Dulmadge EA (1967) Effect of antimetabolites on kinetic behaviour of proliferating cultured L1210 leukemia cells. J Natl Cancer Inst 39: 965