Population pharmacokinetic and adverse event analysis of topotecan in patients with solid tumors

Objective: **Our objective was to describe the pharmacokinetics and pharmacodynamics of topotecan in patients.**

Methods: **Data were pooled from 9 clinical trials. Topotecan, as a single-agent therapy, was administered as a daily 30-minute intravenous infusion for 5 days on a 3-week cycle. Doses of 0.2 to 2.0 mg/m^2 were studied; concentration and neutropenic event data were obtained on multiple occasions. The pharmacokinetics were characterized with use of hierarchical nonlinear regression. The relationship between severity of neutropenia and exposure was characterized with use of logistic regression.**

Results: **The pharmacokinetics of topotecan were described with a linear 2-compartment model. Compromised renal function, low body weight, and poor Eastern Cooperative Oncology Group performance status were determinants of lower clearance, resulting in elevated exposure. Application of covariates reduced interpatient variability in clearance. Logistic regression showed that topotecan area under the concentration–time curve from 0 to 24 hours was predictive of the severity of neutropenia; the only other significant covariate was the number of courses of previous treatment with platinum-based regimens.**

Conclusions: **Patients with compromised renal function, low body weight, or poor performance status had low topotecan clearance. Patients with high topotecan AUC had an increased probability of experiencing severe neutropenia, which was greater if the patient had been pretreated with platinum-based agents. The use of covariates to individualize dose would result in less variability in exposure, reducing the likelihood of severe neutropenia and potentially improving treatment benefit. (Clin Pharmacol Ther 2002;71:334-48.)**

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Topotecan (SKF 104864; Hycamtin) is effective in a number of solid-tumor models that are refractory to other established anticancer drugs. The most commonly evaluated dose schedule for topotecan associated with reproducible antitumor activity was a 30-minute intravenous infusion of 1.5 mg/m^2 administered daily for 5 days every 3 weeks.[1-3] To date, topotecan has been most useful in the treatment of recurrent and refractory ovarian and recurrent small-cell lung cancer.[4,5]

The dose-limiting toxicity of topotecan is hematologic, with severe neutropenia being the most frequently reported toxicity.[3,5] The incidence of grade 4 neutropenia has been reported to be 68%.[6] The median duration of severe neutropenia is typically 1 week or less. In some studies topotecan exposure has been shown to be predictive of the severity of neutropenia.[1,4,7,8] To date, there has been no clear evidence of cumulative hematopoietic toxicity associated with topotecan therapy, and serious clinical sequelae of

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Table I. Patient demographic characteristics for population pharmacokinetic data set

Characteristic	*No. of patients*	*Mean*	*Median*	*Range*
Age (y)	245	58.9	59.0	34-82
Weight (kg)	197	68.5	70.9	36.5-121
Predicted weight (kg)	245	70.3	71.6	37.5-129
BSA (m^2)	245	1.80	1.80	1.3-2.62
CL_{CR} (mL/min)*	244	73.5	68.7	15.5-150
Sex	242			
Male subjects	77	—	—	—
Female subjects	165	—	—	—
ECOG performance status	225			
0	76	—	—	—
1	109	—	—	—
2	39	—	—	—
3	1	—	—	—
Previous or platinum-based treatment	245			
No previous platinum treatment	41	—	—	—
Previous platinum treatment	204	—	—	—

BSA, Body surface area; ECOG, Eastern Cooperative Oncology Group.
*Creatinine clearance (CL_{CR}) was predicted with use of the Cockcroft and Gault formula.[23] Predicted CL_{CR} values higher than 150 were assigned a value of 150 mL/min as a reasonable upper limit for this analysis.[24]

hematologic toxicity such as sepsis, infection, or neutropenic fever are infrequent.[1,7-9]

Topotecan is a lactone that undergoes a reversible pH-dependent hydrolysis to an inactive open ring carboxylate.[5,10] The pharmacokinetic behavior of both the topotecan lactone and total topotecan (topotecan and its open ring derivative) have been characterized and shown to be similar.[1] The population pharmacokinetics of topotecan has been determined and was described with use of a 2-compartment pharmacokinetic model with first-order elimination.[11,12] In those analyses, several demographic and clinical factors, most notably, renal function, were shown to influence the pharmacokinetics of topotecan.[11,12] However, both analyses were conducted with data from a limited number of patients. Furthermore, the relationship between topotecan exposure and adverse events was not examined in those studies.

Topotecan undergoes renal elimination; approximately 20% to 70% of the dose is excreted unchanged.[10,13] In patients with normal renal function, less than 5% of the administered dose is metabolized to *N*-desmethyltopotecan.[4] Additional metabolic pathways for topotecan have been investigated,[10] with *O*-glucuronidation of both topotecan and *N*-desmethyltopotecan accounting for approximately 10% of the administered dose.[14] Other routes of metabolism and elimination for topotecan have not been well established. The pharmacokinetics and clinical toxicity of topotecan have also been evaluated in patients with chronic renal and hepatic impairment.[9,10,15] Those studies concluded that the recommended dose of topotecan should be halved to 0.75 mg/m^2 per day for patients with moderate renal impairment (creatinine clearance [CL_{CR}], 20-39 mL/min). Those studies also showed that the clearance of topotecan was not appreciably diminished in patients with liver dysfunction and that dose reduction was not required for patients with mild or moderate hepatic dysfunction.

The primary objective of this analysis was to model the population pharmacokinetics of topotecan in a large number of patients and to quantitate the ability of age, weight, sex, CL_{CR}, and other patient characteristics to explain the pharmacokinetic variability. Because of missing covariate information in many patients, a joint function approach was used to model the missing values. The second objective was to relate the predicted patient exposure of topotecan with the incidence and severity of neutropenia and to examine the association between patient characteristics and the probability of experiencing an adverse event.

METHODS

Pharmacokinetic data. Data were obtained from 245 patients who were participating in 9 separate phase I, II, and III clinical trials performed during the first 6 years of clinical development of topotecan. The aims of those trials were to assess the safety and effectiveness of topotecan when administered as a 30-minute intravenous infusion given every day for 5 consecutive days on a 3-week dosing cycle. The individual results of these studies have been published previously.[2,9,15,16-22] Patient

Table II. Characteristics of clinical studies used in pooled analysis

Study	*Indication and study type*	*Duration of therapy*	*Doses (mg/m² per day × 5 d)*
1	Solid tumor; phase I[2,22]	Once daily for 5 d every 3 wk; patients were treated for up to 6 cycles	0.5, 0.65, 0.9, 1.0, 1.25, or 1.5
2	Ovarian cancer; phase III[18,22]	Once daily for 5 d every 3 wk; patients were treated for up to 6 cycles	1.5
3	Solid tumor; phase I[16,22]	Once daily for 5 d every 3 wk; patients were treated for up to 6 cycles	1.5
4	Small-cell lung cancer; phase II[19,22]	Once daily for 5 d every 3 wk; patients were treated for up to 6 cycles	1.5
5	Ovarian cancer; phase II[20,22]	Once daily for 5 d every 3 wk; patients were treated for up to 4 cycles	1.5
6	Solid tumor; phase I[9,15,16,22]	Once daily for 5 d every 3 wk; patients were treated for up to 4 cycles	1.5 or 0.75 (depending on renal function)
7	Small-cell lung cancer; phase II[17,22]	Once daily for 5 d every 3 wk; patients were treated for up to 4 cycles	2.0
8	Solid tumor; phase I[22]	Once daily for 5 d every 3 wk; patients were treated for up to 4 cycles	1.5
9	Solid tumor; phase I[21,22]	Once daily for 5 d every 3 wk; patients were treated for up to 6 cycles	0.2, 0.3, 0.4, 0.5

data were included in the pharmacokinetic database provided that the patients had received intravenous topotecan as single-agent therapy during the clinical study.

Table I lists the demographics for the patients included in the pharmacokinetic database. The CL_{CR} was predicted with the Cockcroft-Gault equation.[23] For some patients (n = 3), the predicted CL_{CR} exceeded 150 mL/min, which may have been a result of their high body weights (weight, >100 kg). In such cases, the CL_{CR} was assumed to be 150 mL/min as a reasonable upper limit of this value.[24] One patient had no CL_{CR} information available and was assigned a CL_{CR} value of 70 mL/min. A total of 48 patients (19.6%) had no weight information available. There were 3 patients with no recorded sex and 20 patients (8.2%) with no recorded Eastern Cooperative Oncology Group (ECOG) performance status. Because the number of patients with missing demographic information was high, missing covariates were predicted with use of a joint modeling approach.[25]

A total of 2408 total topotecan plasma concentrations were included in this analysis. The administered doses of topotecan ranged from 0.2 to 2.0 mg/m². A brief listing of the study designs is given in Table II, together with the number of patients from each study with pharmacokinetic data. The average number of samples per patient was 12, collected during 1 to 4 different dosing occasions or treatment cycles. The samples were collected in heparinized tubes and centrifuged at 4°C to separate plasma, which was stored frozen at –30°C until analyzed. Plasma samples were assayed for total topotecan with a method based on protein precipitation with methanol.[26,27] The samples were analyzed by HPLC with fluorescence detection.[26,27] The lower limit of quantitation was 1 ng/mL for the early dose-ranging study[2] and 0.1 ng/mL for all other studies.

Pharmacodynamic data. Data from 438 patients who participated in the same 9 trials included in the pharmacokinetic data set were used to determine the relationship between predicted exposure to topotecan and severity of neutropenia. The number of patients with available adverse event data for each study is given in Table II. Not all patients had pharmacokinetic data available. Consequently, there were more patients in the adverse event data set than in the pharmacokinetic data set. Patients had recorded grades of neutropenia for up to 26 cycles of therapy, although the majority of patients had at least 4 cycles of treatment. The data set contained data from patients with a wide variety of diseases, predominantly ovarian cancer and small cell lung cancer. Only patients receiving single-agent intravenous topotecan administered as a daily 30-minute infusion for 5 consecutive days every 3 weeks were selected. Patient adverse event data were included if complete dosing records and neutropenia adverse event data were available. Patients were excluded if their records indicated that they were receiving drugs that affected hematopoiesis, such as

Pharmacokinetic plasma sampling schedule	*No. of patients with pharmacokinetic data*	*No. of patients with adverse event data*
Days 1 and 4 of cycle 1 at 0, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2.5, 3.5, 4.5, and 6.5 h after start of infusion	18	44
Day 1 of cycles 1, 2, and 3 at 0, 1, 2.5, 4, and 8 h after start of infusion	100	116
Day 1 or 2 of cycle 2 at 0, 5, 15, 30, and 45 min and 1, 2, 3, 4, 6, 8, and 24 h after start of infusion	17	18
Day 1 of cycle 1 at 0, 15, 30, and 45 min and 1, 2, 3, 4, 6, and 8 h after start of infusion	2	54
Day 1 of cycle 1 at 0, 5, 15, and 30 min and 1, 1.5, 2.5, 3.5, 4.5, 6.5, and 8.5 h after start of infusion	3	130
Day 1 of cycle 1 at 0, 15, 30, 35, 45, and 50 m in and 1, 1.5, 2.5, 3.5, 4.5, and 8 h after start of infusion	48	27
Day 1 of cycle 1 at 0, 15, and 30 min and 1.5 and 5 h after start of infusion	33	33
Day 1 of cycle 1 at 0, 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, and 12 h after start of infusion	5	4
Days 1 and 5 of cycle 1 at 0, 18, and 24 min and 1, 1.3, 2.3, 3.3, 4.3, and 5.3 h after start of infusion	19	12

granulocyte colony-stimulating factor. Patient data were also excluded from this data set if CL_{CR}, weight, and ECOG status data were missing. Table III lists the demographic and patient characteristics for the patients included in the adverse event database.

When available, the estimated clearance from the final pharmacokinetic model was used to estimate the individual patient exposure to topotecan. Approximately 43% of the patients included in this data set had at least one estimate of clearance, and 15% of the total adverse event records had an associated individually estimated clearance. For patients with at least one estimated clearance, the geometric mean of estimated clearance was used to predict clearance when an estimate was not available for a cycle in which an adverse event was recorded. When pharmacokinetic data were obtained on more than 1 day of dosing during a treatment cycle, the individual clearance estimate from the first day of dosing was used to be consistent with data obtained from other trials. When no pharmacokinetic data were available for a patient, clearance values were predicted using renal function, weight, ECOG status, and the final population pharmacokinetic parameters (Table IV). Patient topotecan exposure was estimated by dividing the daily dose by either estimated or predicted clearance, as appropriate, yielding an estimate of the area under the concentration–time curve from 0 to 24 hours [AUC(0-24)].

In the majority of studies, white blood cell counts were done once a week (typically before dosing and at 7 or 9 days and at 14 or 16 days after dosing). This number of observations was insufficient to develop a continuous model of neutrophil count with time. Neutropenia was therefore assessed on the basis of grade of neutropenia rather than fitting the time course of neutrophil counts after dose. The lowest absolute neutrophil count during each cycle was graded with use of the National Cancer Institute Common Toxicity Criteria scale (ordered categoric scale from 0 to 4) and was assigned the grade associated with the lowest absolute neutrophil count value recorded for that cycle. A sixth category (scale 5) was also created for adverse events designated as *severe neutropenia with clinical consequence*. This was a subset of patients with grade 4 neutropenia that required medical intervention (eg, neutropenic fever, infection, and sepsis). Although patients with grade 3 neutropenia may be at risk of development of clinical consequences such as neutropenic fever, infection, or sepsis, none of the patients in this data base with grade 3 neutropenia were reported to have clinical consequences. There were 1778 neutropenic event observations (268 with grade 0, 103 with grade 1, 201 with grade 2, 508 with grade 3, 631 with grade 4, and 67 with grade 4 with clinical consequence).

Population pharmacokinetic modeling. A 2-compartment model with first-order elimination from the central compartment was used to fit the concentration–time data. The model was parameterized with use of clearance, volumes of distribution of the central (V_1) and peripheral compartments (V_2), and the intercom-

partmental clearance (Q). To explain the variability in the observed time of peak plasma concentrations, the duration of infusion was also estimated. The influence of patient demographic parameters such as age, predicted CL_{CR}, weight, body surface area (BSA), sex, race, ECOG performance status, and previous treatment with platinum-based regimens as explanatory variables for interpatient parameter variability was assessed with multiplicative covariate models.

The effect of body weight on nonrenal (CL_{NR}) and renal clearance (CL_R), Q, and volumes of distribution was predicted with use of an allometric scaling function.[28,29] The functions for clearance (CL and Q) and volume (V_1 and V_2) are given in equations 1 and 2, respectively:

$$CL = CL_{std} \cdot \left(\frac{wt}{70} \right)^{0.75} \quad (1)$$

$$Volume = Volume_{std} \cdot \left(\frac{wt}{70} \right) \quad (2)$$

Clearance was divided into terms to describe nonrenal clearance ($CL_{NR,\ std}$) and renal clearance ($CL_{R,\ std}$) to reflect the physiologic elimination pathways of topotecan (equation 3). These clearance terms were standardized to a patient weight of 70 kg. The value of predicted CL_{CR} was also standardized to 70 kg and renal function (RF) predicted from this value relative to a standard CL_{CR} in the population of 70 mL/min. This procedure defines renal function independently of body size. ECOG performance status was centered on 1 as follows:

$$CL = (CL_{NR,\ std} + CL_{R,\ std} \cdot RF) \cdot \left(\frac{wt}{70} \right)^{0.75} \cdot \exp^{(\text{Performance Status Factor} \cdot [ECOG - 1])} \quad (3)$$

Covariate model building. A preliminary assessment of covariate influence was conducted with use of the generalized additive modeling approach as implemented in XPOSE.[30] On the basis of results from generalized additive modeling and other mechanistic possibilities, models were built with use of a stepwise forward addition process followed by a backward elimination process. Covariates were included in the model if their statistical significance was $P < .001$, on the basis of the log likelihood ratio test, provided the covariates were reasonable for the pharmacology of the drug. Improvements to the model were also assessed by evaluation of the improvement in agreement between the observed and predicted plasma concentrations, reduction of the terms for interpatient and random unknown variability, reduction in the range of weighted residuals, and uniformity of the distribution of the weighted residuals versus the predicted concentrations about the line of identity.

Joint model for prediction of missing covariate values. Weight, age, CL_{CR}, sex, and ECOG performance status were included in the data set as observations for the purposes of constructing joint models to predict missing covariate data. A function for predicting the missing demographic information was constructed with use of covariates predictive of missing demographics. The function was assessed during the development of the joint model with use of the same model-building approach described for pharmacokinetic model building.

Weight was known to be an important pharmacokinetic covariate but was missing in 19.6% of patients. An empiric function was used to relate BSA, sex, and CL_{CR} to predict weight. The effects of BSA and CL_{CR} were included by use of an exponential model centered on 1.73 m^2 BSA and a CL_{CR} of 70 mL/min. The effect of sex was described by a factor estimated for female subjects in relation to male subjects. Equation 4 describes the final function found to best estimate missing weight. The distribution of interpatient variability for weight and ECOG was described by an additive model, with standard deviation fixed to a value typical of the expected errors in measurement (0.1 kg for weight and 0.1 unit for ECOG).

$$Weight = Baseline \cdot \exp^{(\text{BSA factor} \cdot [BSA - 1.73])} \cdot \exp^{(\text{CLCR factor} \cdot [CLCR - 70])} \cdot \text{Sex factor} \quad (4)$$

Attempts to use the joint model-predicting covariates and topotecan concentrations to estimate the effect of each covariate on pharmacokinetic parameter variability were unsuccessful because there was little or no change in estimated parameter variability when covariates were added. To assess the influence of covariates on parameter variability, the missing covariates were therefore predicted with parameter estimates from the final joint function model. A data set that contained predicted and observed demographic information was then used to estimate the impact of covariates on interpatient pharmacokinetic parameter variability.

Neutropenic adverse events. The severity of neutropenic events in relation to topotecan exposure was evaluated by repeated-measures nonlinear logistic regression.[31-33] The probability of a patient experiencing a neutropenic adverse event was assumed to have no predetermined order for different grades of neutropenic adverse events.

The probability that an adverse event grade Y is less than or equal to an event of grade m (in which m is

Table III. Patient demographic characteristics for adverse event data set

Characteristic	*No. of patients*	*Mean*	*Median*	*Range*
Age (y)	438	58.9	59.0	23.0-85.0
Weight (kg)	438	73.0	68.0	39.0-215
BSA (m^2)	438	1.77	1.73	1.30-2.62
Predicted CL_{CR} (mL/min)*	438	77.5	72.4	6.00-150
Sex	438			
Male subjects	101	—	—	—
Female subjects	287	—	—	—
ECOG performance status	438			
0	161	—	—	—
1	213	—	—	—
2	63	—	—	—
3	1	—	—	—
Previous platinum-based treatment	438			
No previous platinum treatment	71	—	—	—
Previous platinum treatment	367	—	—	—

*CL_{CR} was predicted with use of the Cockcroft and Gault formula.[23] Predicted CL_{CR} values higher than 150 were assigned a value of 150 mL/min as a reasonable upper limit for this analysis.[24]

equal to 0-5) is given by the function described in equation 5 as follows:

$$h(P[Y \leq m|\eta]) = f_{pretreat} - f_{covariate} + \eta_Y \qquad (5)$$

in which h(x) denotes the log odds of an occurrence of a specific grade of neutropenic adverse event, $f_{pretreat}$ is the cumulative log odds of an adverse event grade that occurs in a patient independent of treatment, $f_{covariate}$ is the logit function that describes the effect of a particular covariate, and η_Y is a scalar individual random effect that describes the interpatient variability in the log odds of probability of the predicted grade. Because these neutropenia grades were described with use of a cumulative probability approach, only the cumulative baseline probability for each of the 5 lowest grades of neutropenia (ie, grade 0 to grade 4 with no clinical consequence) was estimated. The sixth grade probability is then implicitly defined because the sum of all probabilities must be 1.

For graphic purposes, data on neutropenic adverse events from all 438 patients were stratified into platinum-naïve and platinum-pretreated groups. The observations within each group were divided into equal-sized bins on the basis of daily topotecan exposure [AUC(0-24)]. The frequency of severity of all grades of neutropenic events was determined for each bin, and these frequencies were superimposed over the estimated probability curves as a means of assessing the descriptive capacity of the logistic model.

Once a base model that described the probability of neutropenic adverse events was defined, exposure as described by dose or AUC was used as a covariate to predict adverse events. The probability function for $f_{covariate\ (treatment)}$ was best described with a hyperbolic relationship (equation 6) as follows:

$$f_{covariate\ (treatment)} = \frac{(AE_{max} \cdot Exposure)}{(E_{50} + Exposure)} \qquad (6)$$

In this equation, AE_{max} is the maximum increase in the cumulative log odds of the occurrence of an adverse event that can be caused by topotecan and E_{50} is the topotecan exposure (ie, dose or AUC) at which half of AE_{max} is reached.

In addition to the covariates examined for the pharmacokinetic model, the influence of the type of disease and the number of previous courses of treatment with platinum-based regimens was examined. In addition, because patients participating in phase I studies have often received more extensive previous treatment and have more advanced disease than patients in later studies, the effect of study phase on adverse event was also assessed. However, data on treatment with other chemotherapeutic agents were not available for this analysis. The acceptance criteria for covariate inclusion into the adverse event model were the same as those used for the pharmacokinetic model.

Once a logistic function that described the probability of neutropenic adverse events was established, credible intervals were generated for the probability curves with use of nonparametric bootstrapping.[34] One thousand bootstrap data sets were created from the original data set, and the model was re-evaluated with the new data sets. The resulting bootstrap parameter estimates were used to reconstruct a family of probability curves. At each AUC value for the curve, the upper and lower 5% values were removed, resulting in 95% credible

Table IV. Population parameters for joint estimation of weight

Parameter	*Estimate*	*Interpatient variability (%)*
Population weight (kg) (θ1)	61.4	
BSA factor (θ2)	0.993	7.46%
Sex factor (θ3)	1.09	
CL_{CR} factor (θ4)	0.000610	

Weight = θ1 · exp(θ2 · [BSA – 1.73]) · exp(θ4 · [CL_{CR} – 70]) · θ3. Random residual variability (additive) = 1 FIX. Sex factor is 1 for male patients and 1.09 for female patients.

intervals for the population mean probability of a neutropenic adverse event in relation to topotecan AUC.

Computational methods. Pharmacokinetic and adverse event data were analyzed with the nonlinear mixed-effects modeling program NONMEM, version V, level 1.1.[35,36] Because the majority of studies included in the pharmacokinetic data set used intensive sampling schedules, the first-order conditional estimation method (FOCE) with the *interaction* option was used.[35] The logistic regression analysis used FOCE with the *Laplace* and *likelihood* options. A convergence criterion of at least 3 significant digits was used.

RESULTS

Joint model for prediction of missing covariate values. The parameter estimates for the parameters in the joint function are given in Table IV. No covariates were identified to be predictive of ECOG status; estimated ECOG performance values were therefore based on the geometric mean of the observed values (ECOG = 1) and the pharmacostatistical model. An exponential model described the terms for interpatient variability for the covariate functions. The covariance of weight, age, CL_{CR}, and ECOG performance status was also used to provide additional information for estimating missing covariate values. Fig 1, *A,* shows the performance of the model in the observed versus predicted patient weights for the joint function that estimated body weight. A linear regression line of observed versus estimated weight suggests that there is no bias in the model because the slope of the line is near unity and the regression coefficient is 0.88. Furthermore, the data are uniformly distributed about the line of unity.

Population pharmacokinetics. The distribution of random unknown variability was best described by a constant coefficient of variation model for all data, with separate additive terms to describe the data obtained from the study assessing the effect of renal and hepatic function.[9,15] The separate additive error term was added because the data from this study had greater apparent random variability and because the patients in this study were sampled more intensively than those in other studies. An exponential model best described interpatient variability of the pharmacokinetic parameters. Interoccasion variability was clearly apparent in the topotecan concentration profiles for patients studied on more than one occasion. Variability in clearance and the central volume therefore included terms to describe the interoccasion variability. For the purpose of this analysis, an *occasion* was defined as the set of concentrations obtained after any single dose. The model was not improved when treatment cycle was used to define an occasion. The inclusion of a term for interoccasion variability in clearance decreased the overall variability in clearance from 54% to 49%.

The final population model included predicted CL_{CR}, body weight, and ECOG performance status as covariates on clearance. On the basis of the estimates of clearance obtained with use of this model, the percentage of total clearance attributed to CL_R in individual patients ranged from 20.7% to 85%. Although the upper end of this estimate is higher than that reported (70%),[10,13] the range of predicted CL_R values is comparable. Furthermore, patients with the higher percentage of CL_R may have been less ill with commensurately better CL_R.

The population pharmacokinetic parameters estimated from the final model are listed in Table V. For a standard patient with a CL_{CR} of 70 mL/min, a body weight of 70 kg, and ECOG of 1, the estimates for CL_{std}, Q_{std}, $V_{1,std}$, and $V_{2,std}$ were 18.6 L/h, 90.4 L/h, 19.2 L, and 44.5 L, respectively. The between-patient variability was 33% for clearance, 64% for Q, and 32% for both V_1 and V_2. The high interpatient variability observed for Q is likely the result of difficulties in evaluating the Q accurately for subjects with sparse pharmacokinetic sampling during each cycle.[18,20] Interoccasion variability was 22% for clearance and 62.9% for V_1. The high interoccasion variability for V_1 is probably reflective of the variable infusion rate. The quality of the final pharmacokinetic model fit is represented graphically in Fig 1, *B* and *C.* The visual agreement between predicted and observed concentrations in Fig 1, *B,* indicates that the model describes the data well. Fig 1, *B,* also suggests that the bias in the final model was generally small, although there were some observations with high weighted residual values. These observations were typically low concentrations. Consequently, a 3-compartment model was evaluated but did not improve the fit of the data. A plot of the individual estimates of clearance from the base model ver-

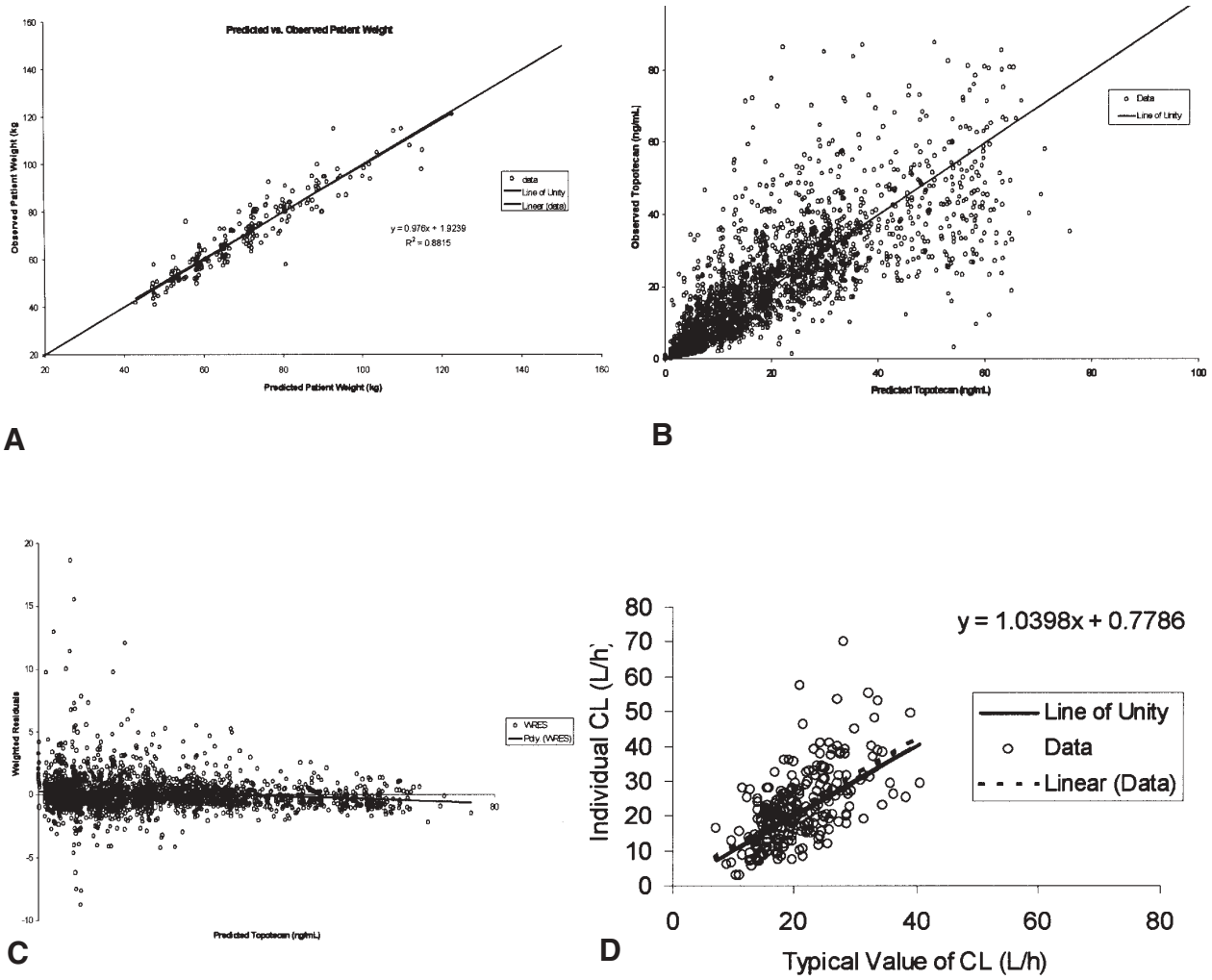

Fig 1. Model performance and diagnostic plots. **A,** Observed versus predicted patient body weights. Predicted patient body weights were obtained from equation 4. **B,** Observed versus predicted plasma topotecan concentration. The *solid line* is the line of unity. **C,** Weighted residuals versus predicted topotecan concentrations. The *solid line* is a linear regression of the data. WRES, Weighted residual; Poly, cubic spline smooth of data. **D,** Typical values of clearance versus individual estimated clearance. The *solid line* is the line of unity and the *broken line* is a linear regression line. The equation shown in the figure is the linear regression of typical versus individual clearance estimates.

sus the typical estimates of clearance from the final model is given in Fig 1, *D*. The plot shows that the typical estimates of clearance are in good agreement with the individual estimates and that there is no apparent bias in the model for predicting clearance.

Effect of drug formulation. During the model-building process, data from an early dose-ranging study[2,22] was found to have plasma concentrations of topotecan that were substantially lower than expected in relation to the dose when compared with later studies. A comparison of the concentration–time data from the 1.5-mg/m^2 dose group from this dose-ranging study and a later study is given in Fig 2. This tendency was observed in nearly all patients in the study. Consequently, all pharmacokinetic parameters associated with patients in this study were substantially higher than those observed in the other patients. This observation was substantiated when noncompartmental pharmacokinetic parameters from this dose-ranging study[2] were compared with noncompartmental pharmacokinetic parameters determined in a representative later study.[16] In addition, the pharmacokinetic parameters obtained

Table V. Population pharmacokinetic parameters of topotecan

		Parameter variability	
Population standard parameters	*Estimate*	*Interpatient*	*Interoccasion*
CL (L/h)		32.7%	22.0%
$CL_{NR, std}$ (θ1)	5.77		
$CL_{R, std}$ (θ2)	12.8		
ECOG performance status factor (θ3)	–0.120		
V_1 (L) (θ4)	19.3	31.8%	62.9%
Q (L/h) (θ5)	90.4	63.6%	NE
V_2 (L) (θ6)	45.7	30.6%	NE
D1 (h) (θ7)	0.435	9.93%	NE
Formulation factor (θ8)	0.489	NE	NE
Random unknown variability (%CV)		18.6%	
Additive component for renal impairment study (ng/mL)		1.01	
Additive component for all other studies (ng/mL)		0.201	

$CL_{NR,std}$, Nonrenal clearance; $CL_{R,std}$, renal clearance; V_1, volume of distribution of the central compartment; V_2, volume of distribution of the peripheral compartment; Q, intercompartmental clearance; D1, duration of infusion; NE, not evaluated. $CL = (\theta1 + \theta2 \cdot RF) \cdot (wt/70)^{0.75} \cdot \exp(\theta3 \cdot [ECOG\ performance\ status - 1])$, in which $RF = CL_{CR}/70$ mL/min · 70 kg/wt. $V_1 = \theta4 \cdot (wt/70)$; $Q = \theta5 \cdot (wt/70)^{0.75}$; $V_2 = \theta6 \cdot (wt/70)$. Standard values: wt = 70 kg; CL_{CR} = 70 mL/min; ECOG = 1.

Table VI. Effect of CL_{CR}, body weight, and ECOG performance status on typical value of CL of topotecan*

		CL (L/h)	
Weight	*CL_{CR} (mL/min)*	*ECOG status 0*	*ECOG status 2*
40 kg	120	21	16
40 kg	30	8	7
80 kg	120	35	27
80 kg	30	14	11
120 kg	120	47	37
120 kg	30	19	15

CL, Clearance.
*A patient with median covariate values (weight of 70.9 kg, CL_{CR} of 68.7 mL/min, and ECOG of 1) has a clearance of 18.5 L/h.

from the dose-ranging study[2] were consistent with reported pharmacokinetic parameters from other studies conducted at approximately the same time (before 1992).[37] In the noncompartmental assessment, the clearance values reported from these early studies were approximately 3 times higher than those in later studies. On review, it was determined that a research drug formulation rather than the marketed formulation was used in the early studies. To account for possible differences in drug formulation, a parameter (analogous to a bioavailability parameter) was added to adjust the apparent dose for patients in this early study. Addition of this parameter to the model resulted in pharmacokinetic parameters that were in better agreement with the parameters obtained in the other studies. Fig 3 shows the improvement in agreement for clearance after the formulation effect parameter was added to the model.

Effect of CL_{CR}, body weight, and ECOG performance status. As expected from previous assessments,[11,12] CL_{CR} had the greatest influence in explaining interpatient variability in clearance. Inclusion of this covariate reduced the interpatient variability on total topotecan clearance from 49% to 40%. Body weight was also found to account for a proportion of interpatient variability, reducing the variability from 40% to 35%. ECOG status accounted for only 2% of the interpatient variability on clearance, reducing the interpatient variability to 33%. No other covariates were found to be significant.

The effect of each of the identified covariates on topotecan clearance can be large. Table VI shows the expected changes in clearance for a number of different combinations of demographic factors. As can be seen, the range of clearances is very wide.

Neutropenic adverse events. The relationship between calculated topotecan exposure and severity of neutropenia grade was described with a nonlinear repeated-measures logistic regression model. The use of a nonlinear function for treatment as a covariate resulted in a lower objective function value compared with a model that used a linear function (ΔOBJ = 35.6).

We tested the hypothesis that concentration rather than dose is a better predictor of neutropenic adverse events by evaluating the data using administered daily dose and BSA-normalized dose. We then compared the results with those obtained with use of AUC(0-24). The

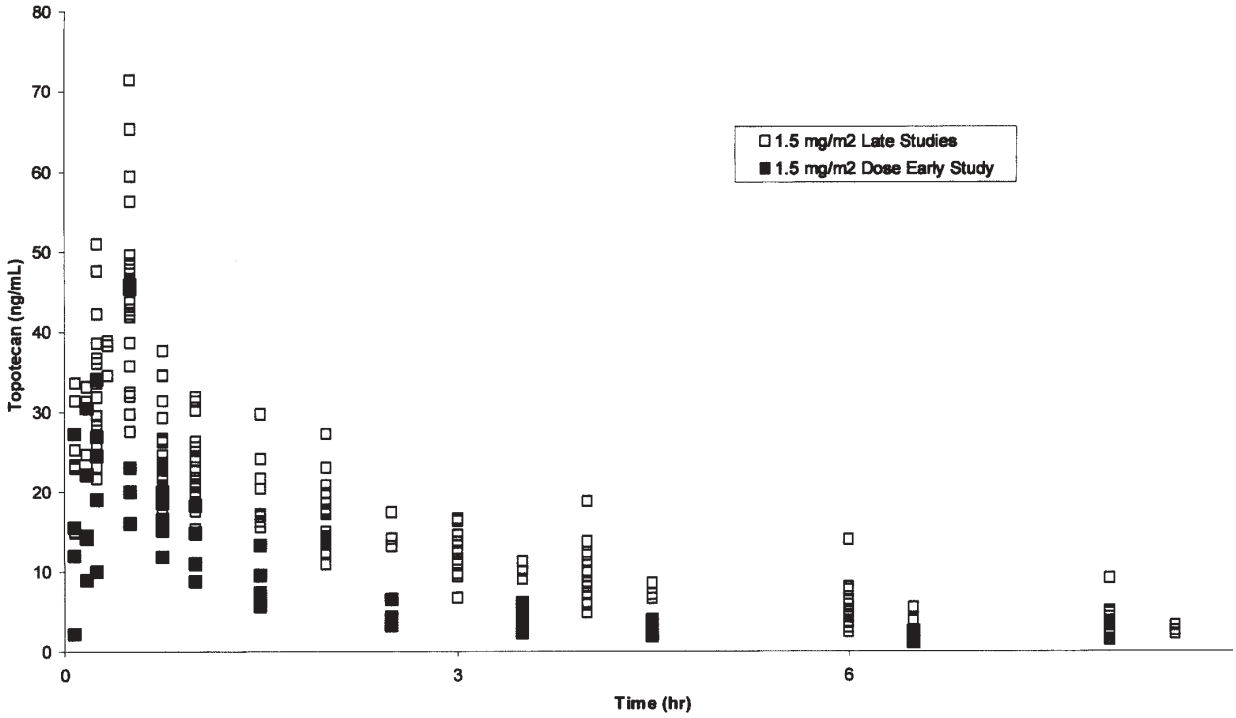

Fig 2. Observed total topotecan concentration–time data from the dose-ranging study[2,22] and a later study.[16,22] The *solid symbols* are data from the early dose-ranging study, and the *open symbols* are from the later study.

Table VII. Population parameters for probability of neutropenic grade with topotecan

Parameter	*Estimate*	*95% CI*	*Interpatient variability (SD)*
Log odds of baseline probability, grade 0 (θ1)	1.46	0.624-2.30	1.012
Log odds of baseline probability, grade 1 (θ2)	0.715	0.561-0.869	
Log odds of baseline probability, grade 2 (θ3)	1.05	0.873-1.23	
Log odds of baseline probability, grade 3 (θ4)	1.92	1.69-2.15	
Log odds of baseline probability, grade 4 (θ5)	3.77	3.35-4.19	
AE_{max} (θ6)	8.16	7.15-9.17	
$E_{50,AUC}$ (θ7)	101	53.1-149	
Platinum effect (θ8)	0.521	0.458-0.584	

CI, Confidence interval; AE_{max}, maximum increase in the cumulative log odds occurrence of an adverse event that can be caused by topotecan; $E_{50,AUC}$, topotecan exposure (ie, area under the concentration–time curve) at which half of AE_{max} is reached. $B0 = \theta1 - (\theta6 \cdot AUC/(\theta7 + AUC)) \cdot$

reduction in objective function was greater with AUC(0-24) than dose (ΔOBJ = 31.0). The difference in objective function between AUC(0-24) and BSA-normalized dose was smaller (ΔOBJ = 7.20). Compared with dose and BSA-normalized dose, the residual between patient variance term was smaller when AUC(0-24) was used. The parameters obtained with use of dose and BSA-normalized dose were comparable to the AUC-based analysis, with similar values for all parameters except E_{50}. The $E_{50,\ dose}$ was 2960 μg, which is equivalent to a dose of 1.64 mg/m^2 for a patient with a BSA of 1.80 m^2. The $E_{50,\ normalized\ dose}$ was slightly lower—1.5 mg/m^2. The calculated AUC(0-24) value associated with both dose-based E_{50} values would be approximately 119 ng · h/mL, which is comparable with the $E_{50,\ AUC}$ (101 ng · h/mL) estimated, suggesting that the $E_{50,\ AUC}$ identified in this study is reasonable.

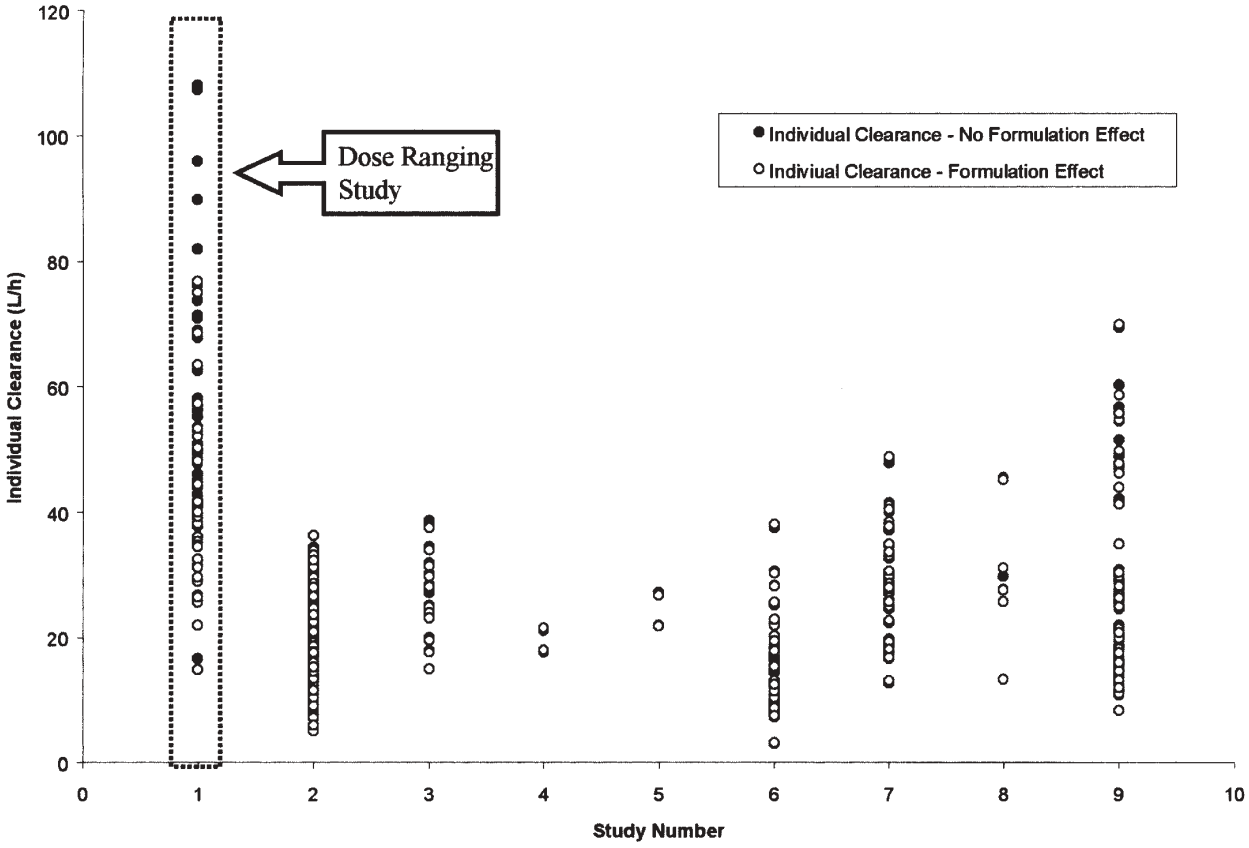

Fig 3. Individual clearance values versus study number. The *solid symbols* are the clearance values obtained without the study effect covariate. The *open symbols* are the clearance values obtained after the formulation effect covariate was applied. The patients in the outlined box participated in the early dose-ranging study.

A potential concern was that topotecan doses might have been systematically reduced with prolonged exposure. Because the risk of an adverse event increases with duration of treatment, the relationship between exposure and adverse event could have been distorted (eg, implying that the probability of an adverse event increases with decreasing exposure). An analysis of administered dose versus cycle of treatment showed approximately a 1% reduction in dose per cycle. This reduction was considered to be insignificant, and it was concluded that dose adjustments attributable to toxicity were not likely to influence the results of this analysis.

After drug exposure, the number of previous courses of treatment with platinum was the only other significant covariate identified in this analysis. Although treatment with cisplatin can alter renal function, the effect of CL_{CR} was not found to be a significant predictor of neutropenia once we had accounted for the effect of renal function on clearance and exposure. The addition of the effect of the number of previous courses of platinum-based therapy resulted in an additional decrease in the objective function of 59.4 points, as well as a reduction in the residual variability term. This reduction was consistent with the reduction in objective function when the effect of platinum was added to the dose and BSA–normalized dose models. The estimates of the model parameters for the AUC(0-24) model are listed in Table VII.

The probability curves for each neutropenic grade in patients who had received one previous course of treatment with a platinum-based regimen (Fig 4, *A, B,* and *C*) and in patients who were platinum-naïve (Fig 4, *D, E,* and *F*) were plotted against topotecan exposure (AUC). The binned observed frequencies of adverse events by grade were superimposed over the probability curves for both patient types. The binned event frequencies are consistent with the probability curves, showing good agreement between the observed fre-

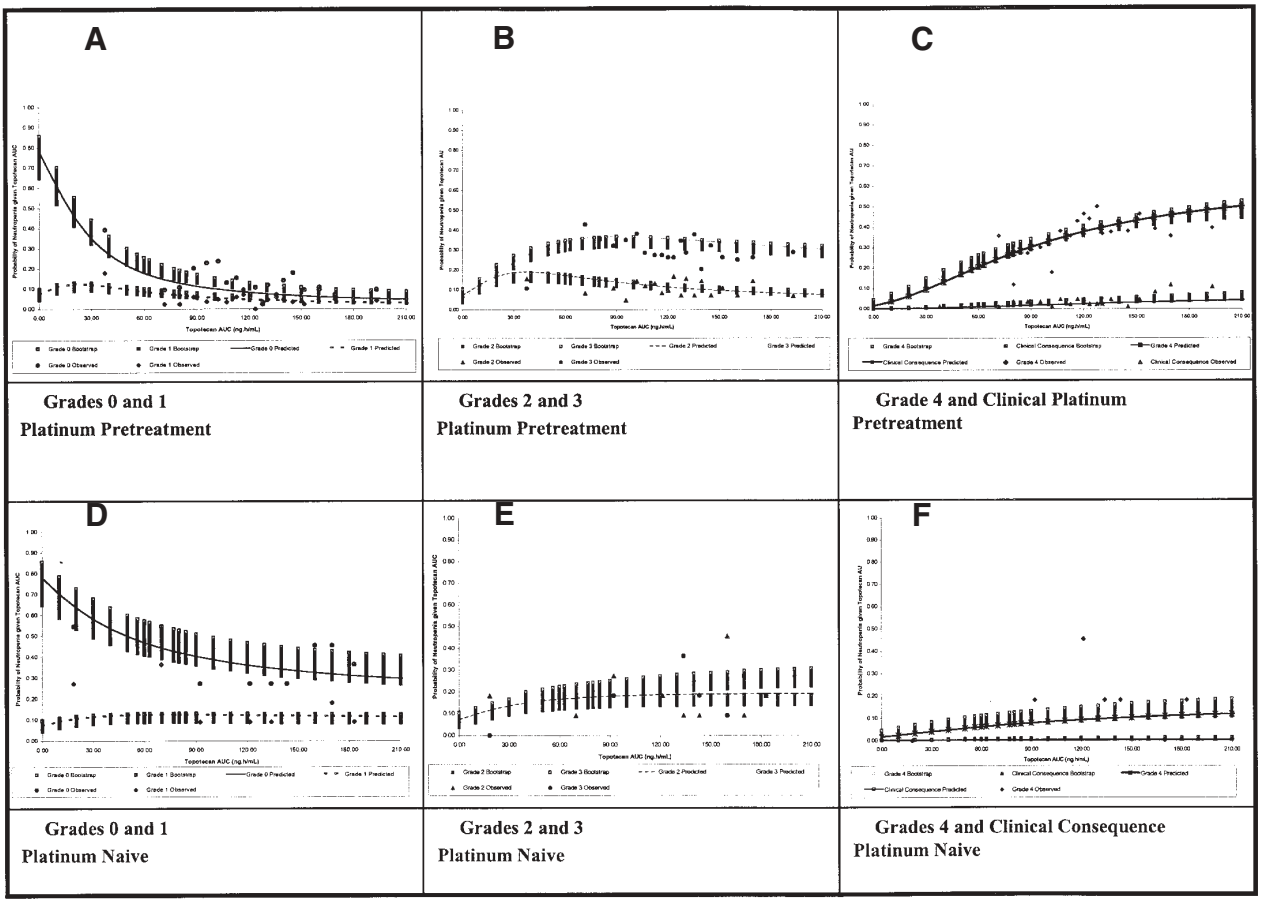

Fig 4. Probability of grade of neutropenic event versus topotecan exposure. **A, B,** and **C,** Predicted probability curves *(lines)* overlaid with binned observed frequencies of neutropenia *(symbols)* for patients receiving 1 course of previous platinum-based therapy. **D, E,** and **F,** Probability curves *(lines)* overlaid with binned observed frequencies *(symbols)* for platinum-naïve patients. The bootstrapped 95% confidence intervals for each probability curve are overlaid as *vertical bars* for all panels.

quency of event and the estimated probability. However, the probability of grade 4 neutropenia with no clinical consequence is underestimated for platinum-naïve patients. The predicted probability curves for each grade of probability are contained within the 95% confidence intervals, and the confidence intervals are reassuringly narrow.

For platinum-naïve patients with topotecan 24-hour exposures up to 90 ng · h/mL, the probability of grade 4 neutropenia was relatively low (<10%), rising to 15% at exposures of 120 ng · h/mL or higher. For patients who previously received at least one course of platinum therapy, the probability of experiencing grade 4 neutropenia was low (<10%) at AUC values of less than 30 ng · h/mL, rising to more than 40% at AUC values that exceeded 120 ng · h/mL. For previously treated patients, relatively small changes in the AUC values resulted in substantial changes in the probability of experiencing a particular grade of neutropenia. Fig 5 depicts the consequences of multiple courses of previous platinum-based therapy on the probability of grade 4 neutropenia (Fig 5, *A*) or neutropenia with clinical consequence (Fig 5, *B*).

Patient sex was not identified as a significant covariate. Consequently, because the majority of female patients had ovarian cancer and the majority of male patients had small cell lung cancer, it is also reasonable to conclude that there is no difference in tolerability between patients with ovarian cancer and patients with lung cancer. Only drug exposure, best characterized by AUC(0-24), and previous treatment with platinum-based regimens were found to be influential covariates.

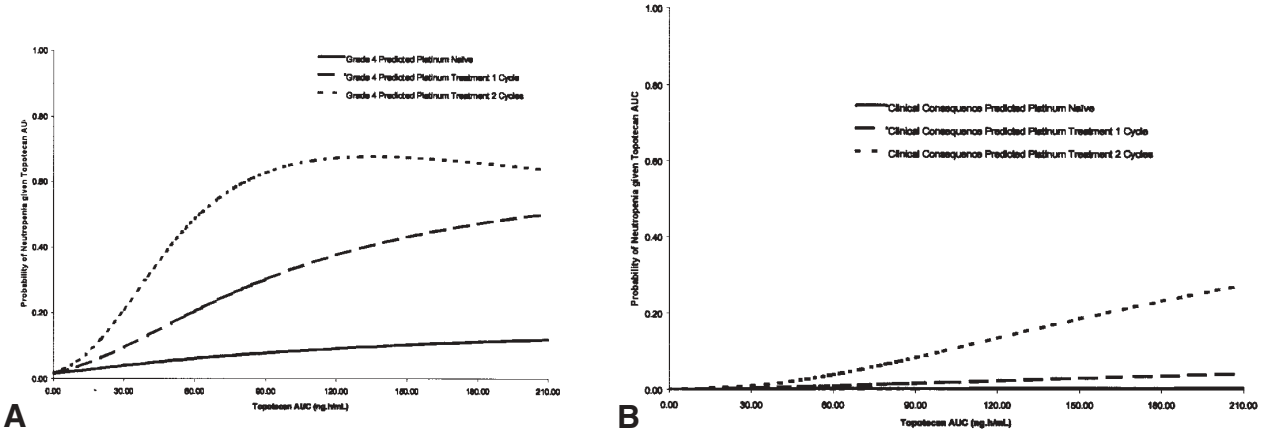

Fig 5. Effect of number of previous courses of platinum-based therapy on the probability of grade 4 neutropenia or grade 4 neutropenia with clinical consequence. AUC, Area under the concentration–time curve.

There was a weak correlation between the number of previous cycles of platinum-based treatment and CL_{CR}; however, the effect of reduced renal function, such as that which may be seen in those patients who had received cisplatin, was accounted for in the estimation of AUC, explaining why renal function was not found to be a statistically significant predictor of adverse events. However, it should be noted that full information, including timing, dose, and treatment with other chemotherapeutic agents used in previous courses of treatment, was not available in this analysis. The platinum effect may therefore be partly confounded with effects from other chemotherapeutic agents. Furthermore, the platinum effect was based on patients receiving either carboplatin or cisplatin because the differences in the effects on the logit function for these two agents could not be discerned.

DISCUSSION

There was a relatively large number of patients (48 of 245) with missing weight observations in the pharmacokinetic data base. A joint modeling method was used to predict the missing weight information on the basis of BSA, CL_{CR}, and sex. This approach is somewhat different than the traditional method of dealing with missing data, such as case deletion (removing incomplete data records) or replacing missing covariate values with median values. Removing incomplete records would have substantially reduced the size of the data set, and that can introduce bias if the missing data are not missing completely at random. The input of missing data by replacing with median values introduced another type of bias in that the distributional characteristics of the covariates were altered. A joint function approach allowed the replacement of missing covariates with reasonable values based on a multivariate function that described the correlations between covariates. Because the pharmacokinetic and joint function models were assessed simultaneously, the joint function approach also allowed the pharmacokinetic information to contribute to the prediction of missing covariates.

The estimated CL_R of topotecan (12.8 L/h per 70 kg) identified in this analysis was large relative to glomerular filtration rate (6 L/h per 70 kg), supporting previous claims that topotecan undergoes tubular secretion.[5,13] Body weight had the second largest impact on the pharmacokinetics, accounting for a small but notable amount of interpatient variability in both clearance and volume parameters. Weight and CL_{CR} were highly correlated because the Cockcroft-Gault equation used to predict patient CL_{CR} uses patient weight. However, the predicted renal function was normalized for weight to remove the effect of body size from the predicted CL_{CR}, thereby separating renal function from body size effects on the clearance of topotecan. Body weight has been previously identified as a predictor of clearance by other authors,[12] and the existing labeling approved by the US Food and Drug Administration for topotecan dosing is based on BSA, which is reflected in body weight. The allometric model[28,29] used in our current analysis to scale the parameters based on weight is similar to BSA.

ECOG performance status was also found to have an effect on the elimination of topotecan, although the number of patients with poor performance status (ECOG 2 or 3) was relatively low in this data set (17.8%). Patients with poor performance status had slightly greater systemic exposure values compared with patients with good performance status. This reduc-

tion in clearance could be caused by a number of factors, including impaired organ function and problems in accurately predicting CL_{CR} in these patients. Predicted CL_{CR} is expected to be an overestimated in cachectic patients with diminished muscle mass.

The reduction in interpatient variability observed when renal function was added to the model is substantial (49% and falling to 40%). The predictable component of overall interpatient variance in clearance with renal function, weight, and ECOG is 47%, whereas the random component is 37%. For renal function, weight, and ECOG performance status, the changes in clearance observed with changes in these covariates result in substantial changes in predicted clearance.

Two other population-based assessments of topotecan pharmacokinetics in adult patients have been published recently.[11,12] These analyses identified covariates similar to those found in this study. The work of Gallo et al[12] in adult cancer patients with solid tumors showed that predicted renal function (with use of serum creatinine, weight, height, and sex) was an important covariate for the clearance of topotecan. Montazeri et al,[11] working on data obtained from patients with ovarian cancer, found that CL_{CR} was the primary covariate.

As shown in the analysis of neutropenic adverse events, elevated exposure to topotecan is associated with an increased probability of grade 4 neutropenia with or without clinical consequences. In a pretreated patient, the probability of a patient having a grade 4 neutropenic event with clinical consequences was predicted to be low at AUC values up to approximately 60 ng · h/mL, rising to more than 10% at AUC values in excess of 150 ng · h/mL. The AUC predicted in a patient with median covariate values (70.9 kg, CLCR = 68.7 mL/min, and ECOG = 1) receiving 1.5 mg/m^2 per day (BSA = 1.80 m^2) was 145.9 ng · h/mL. As a comparison, a patient with good renal function (CLCR = 120 mL/min), a body weight of 70.9 kg, and an ECOG performance status of zero who received the same dose and had the same BSA would have an AUC of 86 ng · h/mL.

The analysis of the neutropenic adverse events in this pooled data set indicated that small changes in patient exposure may result in increased risk of toxicity, particularly if the patient had been heavily pretreated with platinum-based agents. Patients with compromised renal function, low body weight, or poor ECOG performance status may therefore require an adjustment to their doses to reduce the probability of severe neutropenia, at least for the first cycle of treatment, after which the doses can be adjusted upward or downward according to individual tolerability. The results of this analysis are similar to the recommendations for dose adjustments published previously by Armstrong and O'Reilly,[38] who recommended dose reductions based on CLCR, performance status, and heavy pretreatment.

In summary, the findings of the population pharmacokinetic modeling and logistic regression analysis suggest that individualized dosing is appropriate. Patients with compromised renal function, low body weight, or poor performance status have low topotecan clearance. Patients with high topotecan AUC values have an increased probability of severe neutropenia. This probability is higher if the patient has been treated previously with platinum-based agents. The model presented for clearance can be used to calculate an individualized dose to achieve a specified AUC on the basis of individual covariates and previous treatment history. The use of covariates to individualize dose would result in less variability in exposure, reducing the likelihood of severe neutropenia and potentially improving treatment benefit.

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