

A Pharmacodynamic Model for the Time Course of Tumor Shrinkage by Gemcitabine + Carboplatin in Non – Small Cell Lung Cancer Patients

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Abstract **Purpose:** This tumor response pharmacodynamic model aims to describe primary lesion shrinkage in non – small cell lung cancer over time and determine if concentration-based exposure metrics for gemcitabine or that of its metabolites, 2',2'-difluorodeoxyuridine or gemcitabine triphosphate, are better than gemcitabine dose for prediction of individual response. **Experimental Design:** Gemcitabine was given thrice weekly on days 1 and 8 in combination with carboplatin, which was given only on day 1 of every cycle. Gemcitabine amount in the body and area under the concentration-time curves of plasma gemcitabine, 2',2'-difluorodeoxyuridine, and intracellular gemcitabine triphosphate in white cells were compared to determine which best describes tumor shrinkage over time. Tumor growth kinetics were described using a Gompertz-like model. **Results:** The apparent half-life for the effect of gemcitabine was 7.67 weeks. The tumor turnover time constant was 21.8 week-cm. Baseline tumor size and gemcitabine amount in the body to attain 50% of tumor shrinkage were estimated to be 6.66 cm and 10,600 mg. There was no evidence of relapse during treatment. **Conclusions:** Concentration-based exposure metrics for gemcitabine and its metabolites were no better than gemcitabine amount in predicting tumor shrinkage in primary lung cancer lesions. Gemcitabine dose-based models did marginally better than treatment-based models that ignored doses of drug administered to patients. Modeling tumor shrinkage in primary lesions can be used to quantify individual sensitivity and response to antitumor effects of anticancer drugs.

The effect of anticancer drugs on solid tumors is most commonly categorized and reported based on the Response Evaluation Criteria in Solid Tumors Group (1). This method classifies the response of both target and nontarget lesions into four categories: complete response, partial response, progressive disease, and stable disease. It offers a simple criterion that standardizes the measurement and interpretation of tumor

responses across clinical trials, allowing cross-comparison. However, restricting the description of tumor response to these four categories necessarily limits what can be learnt because the tumor size measurement is only used for categorization.

However, the measurement of tumor size provides a continuous scale measure that may be more useful for describing the time course of tumor response in relation to drug exposure. Because tumor growth changes are only observable through repeat follow-up visits and may require sophisticated imaging techniques for accurate measurements in deep-seated tumors, it has yet to gain widespread application as an end point for drug effect modeling in clinical trials. This can be compared with the successful use of changes in hematologic variables on a continuous scale that have been used as pharmacodynamic targets in early-phase clinical trials (2, 3). Therefore, a pharmacodynamic model that directly describes tumor shrinkage effects on the primary lesion(s) of patients may have practical potential as a midterm end point for decision making about effect doses and treatment duration.

Gemcitabine is a synthetic pyrimidine nucleoside antimetabolite anticancer agent with complex metabolic pathways. The parent compound, an inactive prodrug, undergoes deactivation by cytidine deaminase to form its major inactive metabolite 2',2'-difluorodeoxyuridine (dFdU). Extracellularly, a small fraction is also catabolized via a pathway mediated by pyrimidine nucleoside phosphorylase. The remaining gemcitabine and

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dFdU are then transported into the cell and activated intracellularly through progressive phosphorylations by deoxycytidine kinase. The metabolites produced through this process of phosphorylation are the monophosphate, diphosphate, and triphosphate (dFdCTP) forms of gemcitabine, the latter being its active metabolite (4, 5). Observations from previous gemcitabine trials indicated that concentrations of dFdCTP in peripheral blood mononuclear cells can be influenced through manipulation of gemcitabine infusion durations (6, 7). Although this has been postulated to play a part in accounting for neutropenia, whether the same can be said for cytotoxicity of tumor cells, a much delayed effect compared with neutropenia remains unproven.

Gemcitabine has shown activity against a variety of solid tumors, including pancreatic, breast, bladder, and, more recently, ovarian cancers (8). Its most notable effect seems to be in the treatment of advanced non-small cell lung cancer, in combination with a platinum-based compound such as carboplatin or cisplatin (9–12). We have investigated a longitudinal tumor response model to describe and predict the response of the primary lesion in non-small cell lung cancer to gemcitabine chemotherapy. The objectives of this study are to establish a pharmacodynamic model that describes tumor response to gemcitabine and to determine if concentration-based exposure metrics area under the concentration-time curve (AUC) for gemcitabine or either of its metabolites, dFdU or dFdCTP, offer any advantage over gemcitabine dose in describing changes in lung tumor size over time.

Materials and Methods

Patients. The gemcitabine, dFdU plasma concentrations, and dFdCTP intracellular concentrations required to describe the pharmacokinetics of gemcitabine and its metabolites were collected prospectively from a randomized, controlled trial comparing two infusion regimens. Gemcitabine was infused at either a fixed dose rate of 750 mg/m² over 75 min or 1,000 mg/m² over 30 min on days 1 and 8 every 3 wk in stage IIIB or IV non-small cell lung cancer patients (13). Carboplatin dose was administered as a 1-h infusion just before gemcitabine on day 1 of every cycle to patients in both treatment arms based on a target AUC of 5 min·mg/mL. This was considered the first-line treatment for metastatic disease. The study protocol was approved by the institution's Domain Specific Review Board and signed informed consent was obtained from all patients before participation in this study.

Pharmacokinetic and pharmacodynamic data analysis. Computation of population pharmacokinetic variable estimates was done using nonlinear mixed effect regression methods (NONMEM version VI, GloboMax LLC). The first-order conditional estimation method was used with a convergence criterion of six significant digits. The derivation of the clearances for gemcitabine, dFdU, and dFdCTP was based on a four-compartment model using a population approach.⁴ Plasma gemcitabine and dFdU, with intracellular dFdCTP concentrations from peripheral blood mononuclear cells, were used for the pharmacokinetic model. Gemcitabine dose and the AUCs corresponding to each dose given, for gemcitabine, dFdU, and dFdCTP, over the entire duration of gemcitabine treatment were the pharmacokinetic exposure variables. Henceforth, dFdCTP AUC in peripheral blood mononuclear cells will

be referred to as AUC_{dFdCTP}. AUCs for gemcitabine, dFdU, and dFdCTP were derived from individual maximum a posteriori Bayesian estimates of clearance for the parent drug and each metabolite using the following equations:

$$\text{Gemcitabine AUC}_{\text{Gemcitabine}} = \frac{\text{Dose}}{\text{CL}_G}$$

$$\text{dFdU AUC}_{\text{dFdU}} = \frac{\text{CL}_{G2U}}{\text{CL}_G} \times \frac{\text{Dose}}{\text{CL}_{U2O}}$$

$$\text{dFdCTP AUC}_{\text{dFdCTP}} = \frac{\text{CL}_{G2T}}{\text{CL}_G} \times \frac{\text{Dose}}{\text{CL}_{T2O}}$$

whereby CL_G, CL_{G2U}, CL_{U2O}, CL_{G2T}, and CL_{T2O} are clearances for gemcitabine elimination (sum of drug eliminated as gemcitabine itself CL_{G2O}, CL_{G2U}, and CL_{G2T}), gemcitabine conversion to dFdU, dFdU elimination, gemcitabine conversion to dFdCTP, and dFdCTP elimination, respectively.

Serial measurements of the largest dimension of the primary tumor were done on radiological images using electronic calipers at baseline after cycles 2, 4, and 6 and bimonthly thereafter for at least 4 mo after treatment. If multiple measurable lesions were documented, then the sum of the longest unidimensional measurement of each lesion was used throughout the study instead. These tumor size measurements were used as the drug response measure for a pharmacodynamic model. Tumor size measurements extended for a mean of 133 d. This extended observation period results in long computational times, posing limitations on the practicality of simultaneous fitting of drug concentrations and tumor measurements. Changes in the concentrations of gemcitabine and its metabolites occur very rapidly when compared with tumor size changes over time (Fig. 1). For this reason, AUC and drug dosage were used to investigate drug exposure instead of the full time course of drug concentrations.

A schematic representation of the final pharmacodynamic model is depicted in Fig. 2. This Gompertz-like tumor growth model depends on current tumor size and is expected to approach an asymptote (14, 15). Because a delay exists between drug administration and tumor response, the time course of exposure to drug at the tumor effect site was described by a tumor effect compartment half-life ($t_{1/2,eq}$).

$$\frac{d\text{Exposure}}{dt} = -\ln(2)/t_{1/2,eq} \cdot \text{Exposure}$$

At the start of each cycle, either the dose of gemcitabine or the corresponding individual prediction of AUC was introduced into the compartment describing tumor exposure time course. The tumor effect compartment half-life can be thought of as being the apparent elimination half-life of drug from the system after a hypothetical bolus input at the time of each gemcitabine dose (16, 17).

Both E_{\max} and Sigmoid E_{\max} models were tested to describe inhibitory drug effects on tumor growth.

$$E_{\max} \text{ model, Effect} = 1 - \frac{E_{\max} \cdot \text{Exposure}}{\text{Amt}_{50} + \text{Exposure}}$$

$$\text{Sigmoid } E_{\max} \text{ model, Effect} = 1 - \frac{E_{\max} \cdot \text{Exposure}^n}{\text{Amt}_{50}^n + \text{Exposure}^n}$$

Amt₅₀ is a measure of the potency that produces 50% of the maximum inhibition in tumor growth achievable and n is a steepness factor. E_{\max} is the maximum drug effect that was fixed to one because there was no evidence for a smaller maximum effect.

⁴ L.S. Tham et al. Does saturable formation of gemcitabine triphosphate occur in patients? *Cancer Chemother Pharmacol* 2008 Feb 28 [Epub ahead of print].

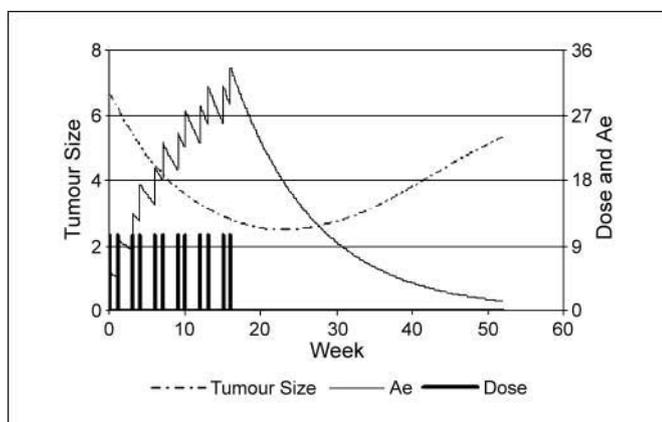


Fig. 1. A comparison of drug dose (thick solid vertical lines), effective exposure (thin solid line), and tumor size measurements (perforated line) on the same time scale measure in weeks.

The final turnover model on tumor size, driven by drug exposure, was

$$\frac{d\text{Size}}{dt} = \left(\text{RateIn} \cdot \text{Effect} - \frac{1}{T_{\text{turnover}}} \cdot \text{Size} \right) \cdot \text{Size}$$

Size refers to unidimensional tumor measurements and RateIn refers to rate of tumor growth at baseline and is defined by the product of the baseline tumor size (Size_0) and $\frac{1}{T_{\text{turnover}}}$. The value of RateIn assumes that there is no net growth of the tumor at baseline. Although this may not be true, we have no good way of estimating baseline tumor growth because there were no serial measurements made before starting treatment. Attempts to estimate the value of RateIn did not improve the goodness fit significantly. T_{turnover} is a second-order time constant for tumor turnover.

It was assumed that all patients had similar exposures to carboplatin and that the contribution of carboplatin to tumor size shrinkage is independent of gemcitabine. A mixture model approach was used to test if there were subgroups of patient with different responsiveness based on the Amt_{50} variable.

Between-subject variability of the pharmacodynamic variables was described by an exponential model for random effects. Model discrimination was based on changes of the objective function value (OBJ) of NONMEM. A decrease in OBJ (ΔOBJ) of >3.84 corresponds approximately to a P value of <0.05 for nested models differing in one variable. Evaluation of the final pharmacodynamic model was done using a visual predictive check procedure. The time course of tumor response was simulated with 500 replications of the original patient data set and the median and 90% prediction intervals were compared with the observed median and 90% observation intervals. A bootstrap using 1,000 replicated data sets, generated by sampling with replace-

ment, was done to obtain the 95% confidence intervals of the model variables for the final model.

Results

A total of 202 tumor size measurements from 56 patients were used to establish the pharmacodynamic model for tumor response. The mean period of tumor size follow-up and its SD were 132.9 ± 113.1 days. Table 1 lists the patient characteristics, median values for dose, and empirical Bayesian estimate of AUC for gemcitabine. The shrinkage for the empirical Bayesian estimate for gemcitabine clearance was 12.5%.

The $\text{Dose}_{\text{gemcitabine}}$ model (OBJ = 455.674) was better in terms of OBJ when compared with a model based on $\text{AUC}_{\text{gemcitabine}}$ (OBJ = 458.027). Neither intracellular AUC, dFdCTP (OBJ = 457.988), nor the inactive metabolite dFdU AUC improved the fit (OBJ = 459.056). A mixture model that allowed up to three subgroups (responders, partial responders, and poor responders) did not show any significant improvement in the objective function (453.560). Because all patients received carboplatin, a model driven by carboplatin dose was tried. The fit was not as good when carboplatin dose alone was used (OBJ = 457.750). A model with both carboplatin and gemcitabine dose improved the fit but not significantly (OBJ = 452.963). In general, the Sigmoid E_{max} models did only marginally better than the E_{max} models, but this was not enough to accept the Sigmoid E_{max} model as the final model.

Table 2 lists the pharmacodynamic variable estimates and their 95% confidence intervals. A gemcitabine amount in the body (Amt_{50}) of 10,600 mg is required to achieve a 50% reduction in tumor growth rate. Between-subject variability of 146% in Amt_{50} was determined in this cohort of patients. Figure 3 shows the visual predictive check of tumor size over the time periods of 16 and 52 weeks and their 90% prediction intervals. It was apparent that tumor size measurements exhibited an initial reduction following the onset of chemotherapy. This effect was sustained for a period of time even after chemotherapy was completed, after which a gradual increase was seen. Only three patients (6%) showed initial response to chemotherapy followed by possible tumor regrowth. There was no clear evidence for resistance during treatment in any patient.

Discussion

An empirical pharmacodynamic model describing tumor size changes over the time course of chemotherapy with sparsely sampled tumor size measurements was applied to various

Fig. 2. A schematic representation of final pharmacodynamic model: k_1 , first-order rate constant for effect equilibration, expressed as ($k_1 = \frac{\ln 2}{t_{1/2,eq}}$), k_2 , second-order rate constant for tumor loss, expressed as ($k_2 = \frac{1}{T_{\text{turnover}}}$); Amt_{50} , gemcitabine dose required to produce 50% of maximum inhibition in tumor growth achievable; E_{max} , maximum gemcitabine effect on tumor is fixed to 1.

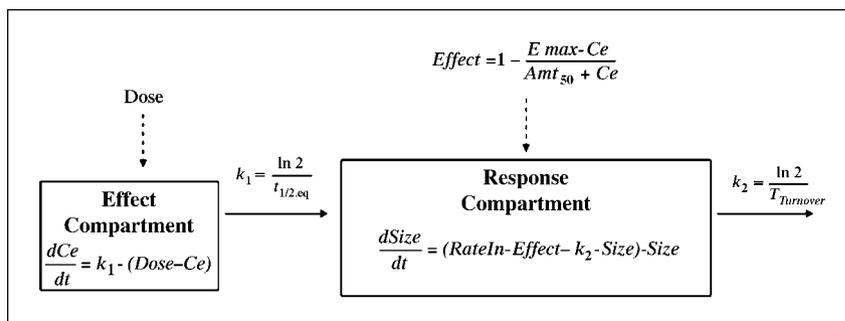


Table 1. Patient characteristics

	Mean
Age, y (\pm SD)	58.2 \pm 9.7
Sex	
Male	39
Female	17
Race	
Chinese	45
Malay	10
Indian	0
Other	1
Cancer staging	
IIIB	9
IV	47
Karnofsky performance status	
70-80%	11
90-100%	45
Weight, kg (\pm SD)	58.1 \pm 11.9
Height, m (\pm SD)	1.61 \pm 0.08
CLcr, mL/min (\pm SD)	74.7 \pm 18.9
Smoking history	
Current smoker	10
Ex-smoker	21
Nonsmoker	25
	Median (range)
Gemcitabine dose (mg)	1,382.5 (975-1,990)
Gemcitabine AUC (μ g·h/L)	5,074.9 (2,904.8-10,589.8)

pharmacokinetic measures of gemcitabine exposure to explore whether the active intracellular dFdCTP is predictive of gemcitabine action. Gompertz (14) and similar models have been used successfully in the evaluation of tumor growth dynamics in many *in vitro* studies of tumor growth kinetics both in animals and in cell lines (18–22).

In this model, we tried to find evidence in the data to identify the baseline tumor growth rate but the best fit is very close to the assumption that the growth rate is determined by the size at baseline. We accept that this is an assumption of our model. Substantive extrapolations from the model should include tests of sensitivity to this assumption. However, our report at this stage is descriptive and intended to stimulate further research, which may be able to improve on this assumption. A limitation of the model is that, because a combination chemotherapy

regimen was given, the tumor responses attributable to gemcitabine cannot be distinguished from that of carboplatin. The extent of tumor shrinkage was predictable by a gemcitabine dose-driven model, which was as least as good as that seen using parent gemcitabine exposure ($AUC_{\text{gemcitabine}}$). It would be expected that individualization of the intensity of drug exposure based on individual gemcitabine pharmacokinetics would provide a stronger association with response. However, between-subject variability in gemcitabine clearance was relatively modest (32%), which means it would have a negligible contribution to the overall dose-response variability described by the 146% variability in Amt_{50} . There is therefore no reason to believe that a target concentration approach would be helpful in dose individualization for gemcitabine. The onset of tumor response was slow in relation to changes in drug exposure; hence, an effect compartment model was used to describe the delayed effects on tumor growth. The delay in tumor size changes may be attributed to diffusion of gemcitabine into cells, conversion to the presumed active metabolite, binding to DNA, modification of tumor protein turnover, cell death, and removal of dead cells.

We found no clear evidence of tumor regrowth during gemcitabine treatment. This is in contrast to a brief report of a similar tumor growth model for the action of capecitabine and docetaxel (23). That model is said to include a component for drug resistance but the “resistance” part of the model is almost identical to the effect compartment model we have used. The resistance model seems to imply that the effect of each dose of drug would continue indefinitely in the absence of resistance. We have preferred to believe that the effect of each dose will eventually wear off as the consequence of drug exposure disappears from the system.

Although the confidence intervals and between-subject variability for Amt_{50} are wide, a mixture model consisting of responders, partial responders, and poor responders did not provide any further explanation for this variability. Hence, this E_{max} tumor response model was considered to be applicable across the spectrum of tumor responses seen in this study.

We failed to find any direct confirmation that dFdCTP, the active metabolite of gemcitabine, is a better predictor than gemcitabine dose alone. This could be due to the estimation error in AUC_{dFdCTP} because of the limited duration of sampling in relation to the apparent half-life in white cells (13) or

Table 2. Final median estimates and 95% confidence intervals of gemcitabine dose-driven pharmacodynamic model variables from 988 successful runs at the bootstrapping final model

Variable	Estimate		Between-subject variability	
	Median	95% CI	%	95% CI
Size ₀ , tumor size measurement at baseline (cm)	6.66	5.66-7.77	55.6	45.1-66.1
T_{turnover} , tumor turnover (cm·week)	21.8	7.97-83.8	23.1	0.58×10^{-5} to 93.0
Amt_{50} , gemcitabine dose at 50% tumor size shrinkage (mg)	10600	705-19,897	146	85.9-300
$t_{1/2,eq}$, effect equilibration half-life (wk)	7.67	1.07-17.6	—	—
Residual error				
Proportional error	0.185	0.094-0.268	—	—
Additive error	0.117	0.001-0.327	—	—

Abbreviation: 95% CI, 95% confidence interval.

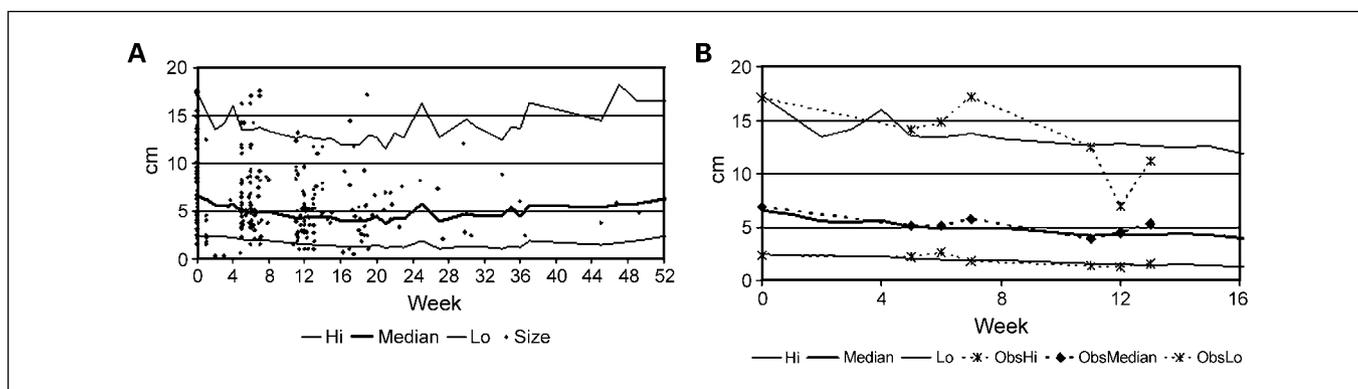


Fig. 3. Evaluation of the final pharmacodynamic model through a visual predictive check of a simulated data set of 500×56 patients. Perforated lines, observations; solid lines, predictions. *A*, scatter plot of actual tumor size observations (solid circles), median values, and 90% prediction intervals (solid lines) of a simulated data set over 52 wk. *B*, plot of median values of observed tumor sizes and 90% observation intervals (solid lines) versus median values of simulated tumor size predictions and their 90% prediction intervals (perforated lines) over 16 wk.

because the kinetics of tumor dFdCTP are not well correlated with the formation of the metabolite in white cells. The results of this model did not support the use of intracellular concentrations of the active metabolite of gemcitabine, dFdCTP, in peripheral blood mononuclear cells as an indicator of dFdCTP activity in tumor cells. Although *in vitro* and *in vivo* studies on intracellular dFdCTP concentrations may suggest its role in hematologic toxicity (24–26), it is still unknown whether the pharmacokinetics of dFdCTP in white cells can be extrapolated to tumor or even normal tissue cells (27). dFdCTP concentrations were just detectable in head and neck tumor samples obtained through biopsy when gemcitabine was given at a dose of 10 mg/m^2 (28), but this study did not examine dFdCTP concentrations in white cells. The implications of the current study indicated that further investigations of the antitumor mechanisms of gemcitabine are warranted because pharmacokinetics of its active intracellular metabolite, dFdCTP, in peripheral blood mononuclear cells may not be a model that closely mimics its antitumor behavior.

Tumor measurements used in this study were recorded for computing tumor response based on the Response Evaluation Criteria in Solid Tumors criteria. These criteria based on unidimensional measurement of both target and nontarget lesions have been shown to exhibit good correlations with bidimensional metrics. This justifies our use of a unidimensional measure of tumor size for response modeling (1). Further, it has been proposed that changes in tumor diameter better describe the rate of cells killed by a standard dose of chemotherapy compared with a bidimensional metric from the product of the longest diameter of a tumor and its longest perpendicular diameter (29, 30). This has been shown to correlate well with actual three-dimensional tumor volumes measured by helical computer tomography (31). The bidimensional metric originally advocated by the WHO has not been

widely adopted because of its laborious and error-prone method for calculations (32). Because tumor measurements are often conducted at baseline and specific intervals as indicators of treatment response in early-phase clinical trials, tumor response models can provide valuable information without adding substantial investigational costs. In addition, precision of estimating tumor size can be further improved in future studies with the use of advanced multislice computed tomography scanning methods to reconstruct exact tumor volumetry.

Conclusion

The results of this study showed that a gemcitabine dose was equivalent to gemcitabine AUC and better than AUC-driven models of gemcitabine metabolites in predicting tumor size changes during and after multiple cycles of gemcitabine chemotherapy with carboplatin. Although survival analysis remains the mainstay for evaluating drug effectiveness in phase III studies, tumor models such as the one presented in this study provide practical insight into the potency and time course of anticancer agents in shrinking primary tumors. More importantly, this can be done with data routinely obtained during early phases of clinical trials and could add valuable information to decision making in drug development. A combination of tumor response model that describes the extent of antitumor effects with toxicity models such as the Friberg myelosuppression model (2, 3) makes a model-based approach to optimal design of chemotherapeutic drug regimens seems feasible.

Disclosure of Potential Conflicts of Interest

The author has conflict with Eli Lilly.

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