Pharmacodynamic Model of Topotecan-induced Time Course of Neutropenia


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ABSTRACT
Pharmacodynamic measures of neutropenia, such as absolute neutrophil count at nadir and neutrophil survival fraction, may not reflect the overall time course of neutropenia. We developed a pharmacokinetic-pharmacodynamic model to describe and quantify the time course of neutropenia after administration of topotecan to children and to compare this with nonhuman primates (NHPs) as a potential preclinical model of chemotherapy-induced neutropenia. Topotecan was administered as a 30-min infusion daily for 5 days, repeated every 21 days. As part of a Phase I Pediatric Oncology Group study, topotecan was administered at 1.4 and 1.7 mg/m2/day without filgrastim (POG), and at 1.7, 2, and 2.4 mg/m2/day with filgrastim (POG+G). In NHPs, topotecan was administered at 1.5 mg/m2/day as a 30-min infusion for 5 days repeated every 21 days (3, 4). The primary dose-limiting toxicity associated with topotecan on this schedule is neutropenia (3–5). Moreover, the primary dose-limiting toxicity of many anticancer agents is bone marrow suppression (6–8). At present there are no reliable in vivo preclinical models of chemotherapy-induced bone marrow suppression (9–11). However, NHPs3 are a good model of radiation-induced bone marrow suppression and may be an appropriate model of chemotherapy-induced neutropenia and thrombocytopenia (10). Thus, we evaluated pharmacodynamic factors associated with topotecan-induced neutropenia in a NHP model and compared those data with data from a Pediatric Oncology Group Phase I study of topotecan (12).

Patients with prolonged neutropenia have a greater risk of infection than do patients who develop the same neutrophil nadir but rapidly recover their neutrophil count (6–8). Previous pharmacodynamic analyses of anticancer agents have used a linear, log-linear, or Emmax model to describe the relationship between drug peak concentration or exposure (measured as the AUC or steady-state concentration), the number of neutrophils at nadir, and the percentage decrease in absolute neutrophil count (11, 13). Previously, we reported a steep relationship between topotecan systemic exposure and toxicity (depicted as the percentage decrease in absolute neutrophil count; Refs. 12, 15). However, the percentage decrease in neutrophils may not

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1 The abbreviations used are: NHP, nonhuman primate; AUC, area under the concentration-versus-time curve; $k_{\text{MAT}}$, rate constant describing the maturation and movement of neutrophils from the bone marrow to the blood; $k_{\text{SN}}$, rate constant describing the distribution of drug to and from the bone marrow; $k_{\text{PS}}$, rate constant describing stem cell production; $k_{\text{PS}^+}$, rate constant describing half-life of neutrophils in peripheral blood; ABC, area between the neutrophil survival fraction-versus-time profile that would occur without treatment and that measured after treatment with topotecan; MPE, mean predictive error; RMSE, root mean square error.
reflect the duration of toxicity or incorporate the time delay between drug administration and the occurrence of toxicity. Compared with the pharmacodynamic modeling of other drugs with immediate effects, modeling the myelosuppressive effects of anticancer agents must include parameters that describe the production as well as the destruction of the target cells. Pharmacodynamic measures of chemotherapy-induced neutropenia over the entire treatment cycle may provide important information. Thus, we developed a pharmacodynamic model to describe the time course of the neutrophil survival fraction in children compared with NHPs as a potential preclinical model of neutropenia after administration of topotecan daily for 5 days, repeated every 21 days.

PATIENTS AND METHODS
Patient and Subject Population. The topotecan lactone plasma concentrations and absolute neutrophil count for children were obtained from a Phase I study of topotecan in children with refractory solid tumors (POG9275; Ref. 12). The POG study was approved by the institutional review board at each of the collaborating institutions. The pharmacokinetic and pharmacodynamic studies were performed on cycle 1 only. In this Phase I study, topotecan was administered as a 30-min infusion daily for 5 consecutive days, repeated every 21 days. The dosages of topotecan evaluated were 1.4 and 1.7 mg/m²/day without subsequent filgrastim and 1.7, 2.0, and 2.4 mg/m²/day with subsequent filgrastim. Filgrastim was administered at 5 (n = 3), 10 (n = 3), and 20 (n = 3) mg/m²/day as a 30-min infusion for 5 consecutive days, repeated every 21 days. Pharmacokinetic studies were performed on three NHPs per dosage group. However, because of logistical issues, we were only able to perform pharmacodynamic studies on two NHPs per dosage group.

Blood Counts. Absolute neutrophil counts were measured at least twice per week and every other day in the pediatric and NHP studies, respectively. The absolute neutrophil survival fraction was calculated as the ratio of the lowest absolute neutrophil count measured on days following treatment to the absolute neutrophil count on the day prior to the start of treatment.

Pharmacokinetic Sampling and Processing. Blood samples for pharmacokinetic analysis were obtained on day 1 of cycle 1 in the pediatric and NHP studies. For each study, blood samples were obtained before and at 0.25, 0.5, 1, 1.5, 3, and 6 h after the end of the topotecan infusion. At each time, 3 ml of blood were obtained from a site contralateral to that of i.v. administration and placed into heparinized tubes. Within 2 min, blood samples were centrifuged at 2000 × g for 2 min, after which 200 µl of plasma were added to 800 µl of cold methanol (-20°C), vortexed for 10 s, and centrifuged at 2000 × g for 2 min. The resulting methanolic supernatant was decanted and stored at -70°C until analyzed.

Plasma topotecan concentrations were measured by a previously described isocratic high-performance liquid chromatography assay using fluorescence detection (12, 17, 18). The methanolic supernatant was used to measure topotecan lactone concentration. The total topotecan total (sum of lactone and hydroxy acid) concentration was measured by adding 20 µl of 20% phosphoric acid to 400 µl of the methanolic supernatant.

Pharmacokinetic and Pharmacodynamic Analysis. A pharmacokinetic-pharmacodynamic model was fit to the profiles of topotecan lactone plasma concentration versus time and...
the neutrophil survival fraction versus time (Fig. 1). This was accomplished using maximum likelihood estimation in the ADAPT II modeling program (19). Individual parameters estimated in the two-compartment pharmacokinetic section of the model included the volume of the central compartment (Vc), the intercompartmental rate constants (k12 and k21), and the elimination rate constant from the central compartment (k10). Individual parameters and standard equations were used to calculate systemic clearance (Clsys) and elimination half-life (t1/2; Refs. 19, 20). Individual parameter estimates were used to calculate the area under the topotecan lactone (AUCLAC) and total (AUCTOT) plasma concentration-versus-time curves from zero to infinity, using the log trapezoidal method (19). The ratio of topotecan lactone to total form was calculated as the ratio of AUCLAC to AUCTOT. For the pharmacodynamic analysis, the topotecan lactone AUC from 0 to 120 h was calculated from the simulated concentration-versus-time profile from 0 to 120 h (i.e., after five consecutive daily doses) based on the day 1 pharmacokinetic parameters.

The pharmacodynamic section of the model was modified from an Indirect Response Model with production linked to an effect compartment (IRMLINK) in the ADAPT Model Library (19, 21). In our model, the concentration of topotecan in the bone marrow was defined as compartment-3, the effect compartment in which topotecan inhibits stem cell production was defined as compartment-4, and the measured reduction in absolute neutrophil count in the blood was defined as compartment-6. In addition, a delay compartment (compartment-5) and the rate constant describing the maturation and movement of neutrophils from the bone marrow to the blood (k34) were used to represent the time delay between the inhibition of stem cell production by topotecan and the measured effect on neutrophil count in the blood. The delay compartment and rate constant used to describe time delay were modified from the delay-chain model used to describe oral absorption of phosphates in rats (22). In the model development, the number of delay compartments varied from 1 to 10; however, a single delay compartment produced the best fit of the data.

Additional individual parameters estimated in the pharmacodynamic section of the model included the rate constant describing the distribution of drug to and from the bone marrow (k65), the rate constant describing stem cell production (k50), the concentration of topotecan that inhibits k50 by 50% (IC50), and the rate constant describing the half-life of neutrophils in peripheral blood (kOUT). The half-life of neutrophils in peripheral blood corresponds to a kOUT of 0.099 h^-1 (22). Chemotherapy does not affect the half-life of neutrophils; thus, in our model the kOUT was fixed at 0.099 h^-1 for each subject. At baseline the kIN = kOUT; thus, the initial estimate of kIN was 0.099 h^-1, and a final parameter value was estimated for each subject.

The area (ABC) between the neutrophil survival fraction-versus-time profile that would occur without treatment and that measured after treatment with topotecan from 0 to 700 h is depicted in Fig. 2. The ABC was calculated by the log-trapezoidal method. The degree of neutropenia associated with plasma drug exposure was calculated as the ratio of ABC to AUCLAC from 0 to 120 h.

Model Evaluation and Statistical Analysis. The predictive performance of the model was determined by the MPE, RMSE, and residuals. The Mann-Whitney test was performed on kIN, IC50, neutrophil nadir, ABC, and the ratio of ABC to AUCLAC, using StatXact-3 software (Version 3.1; Cytel Software Corp., Cambridge, MA).

RESULTS

Topotecan Pharmacokinetics in NHPs. The mean ± SD model fits (i.e., R^2) to the topotecan lactone and total plasma concentration-versus-time profiles were 0.98 ± 0.01 and 0.97 ± 0.02, respectively. The pharmacokinetic parameters for topotecan lactone and total topotecan are summarized in Tables 1 and 2, respectively. The ratios of AUCLAC to AUCTOT at 5, 10, and 20 mg/m^2 were 0.57 ± 0.06, 0.52 ± 0.05, and 0.37 ± 0.06, respectively. The ~2-fold reductions in topotecan total clearance and the ratio of AUCLAC to AUCTOT suggest nonlinear clearance of the inactive hydroxy acid between topotecan doses of 10 and 20 mg/m^2.

Absolute Neutrophil Count Survival Fraction at Nadir. The neutrophil survival fractions at nadir for children administered topotecan with and without subsequent filgrastim and in
NHPs administered topotecan without filgrastim are represented in Fig. 3. The mean ± SD (median; range) neutrophil survival fraction at nadir in children administered topotecan with and without subsequent filgrastim and in NHPs administered topotecan without subsequent filgrastim were 0.11 ± 0.17 (0.05; 0.0–0.56), 0.12 ± 0.09 (0.12; 0.01–0.30), and 0.09 ± 0.08 (0.10; 0.01–0.25), respectively. The differences for neutrophil survival fraction at nadir among all groups were not statistically significant (P > 0.05).

**Pharmacodynamic Model of the Time Course of Neutrophil Survival Fraction**. The pharmacodynamic analysis was performed on 10, 11, and 6 subjects from children administered topotecan with and without subsequent filgrastim and in NHPs administered topotecan without subsequent filgrastim, respectively. The mean ± SD (median; range) number of pharmacodynamic data points (i.e., survival fraction of neutrophils) per subject from children administered topotecan with and without subsequent filgrastim and from NHPs administered topotecan without subsequent filgrastim were 9.3 ± 2.6 (10; 6–15), 7.9 ± 2.9 (7; 5–14), and 8.9 ± 0.7 (9.0; 8–10), respectively. The greater number (i.e., >10) of pharmacodynamic data points for some patients administered topotecan with and without filgrastim was attributable to prolonged neutropenia. However, the model fit of the data was similar for subjects with a short duration of neutropenia and few neutrophil measurements (e.g., n = 5) compared with subjects with a prolonged duration of neutropenia and a greater number of neutrophils (e.g., n > 10). In addition, patients with neutropenia lasting longer than the 21st day (i.e., 504 h after the start of treatment) of cycle 1 were delayed in receiving cycle 2. Thus, the ABC was calculated from 0 to 700 h in all patients and NHPs.

A representative time course and model fit of the neutrophil survival fraction in a patient administered topotecan without subsequent filgrastim are represented in Fig. 4. A representative time course and model fit of the neutrophil survival fraction in a NHP administered topotecan without subsequent filgrastim are represented in Fig. 5. The mean ± SD model fits (i.e., R²) of the neutrophil survival fraction in children administered topotecan with and without subsequent filgrastim and in NHPs administered topotecan without filgrastim were 0.85 ± 0.08, 0.85 ± 0.18, and 0.80 ± 0.21, respectively. The MPEs for all data, for children administered topotecan with and without subsequent filgrastim, and for NHPs administered topotecan without subsequent filgrastim were −0.08 ± 0.15, −0.10 ± 0.12, −0.06 ± 0.15, and −0.07 ± 0.10, respectively. The RMSE for all data, for children administered topotecan with and without subsequent filgrastim, and for NHPs administered topotecan without filgrastim was 0.28, 0.32, 0.24, and 0.26, respectively. Residuals of prediction (predicted surviving fraction − observed surviving fraction) plotted against time for all patients after the start of topotecan are presented in Fig. 6. Negative residuals from 0 to 96 h were explained by the inherent variability in neutrophil counts at baseline and immediately after administration and by transient increases in neutrophils after topotecan administration. Negative residuals occurring ≥384 h after the start of treatment were explained by transient increases in neutrophils during recovery and an overshoot of neutrophil counts observed in some patients.

Parameters describing the pharmacodynamic model of topotecan-induced neutropenia are presented in Table 3. The kout, ABC, and kinp between the three groups were not statistically different (P > 0.05). However, the difference between the ratio of ABC to AUC_{LAC} for NHPs administered topotecan without filgrastim was statistically significantly different (P < 0.05) from those for children administered topotecan with or without filgrastim. The ratio of ABC to AUC_{LAC} is represented in Fig. 7. In addition, the difference between kIN for NHPs administered topotecan without filgrastim was statistically significantly different (P < 0.05) from those for children administered topotecan with or without filgrastim. The differences between the ratio of ABC to AUC_{LAC} and kIN for children administered topotecan with and without filgrastim were not statistically significant (P > 0.05). The IC_{50} for children administered topotecan without filgrastim was significantly (P < 0.05) lower than those for children administered topotecan with filgrastim and the NHP group. Ultimately, the lack of an impact of filgrastim on the degree of neutropenia and ABC may be attrib-

**Table 2** Topotecan total pharmacokinetic parameters in a NHP model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>5</th>
<th>10</th>
<th>20</th>
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<tbody>
<tr>
<td>AUC (ng/ml/h)</td>
<td>324.7 ± 120.1</td>
<td>562.0 ± 162.2</td>
<td>1808.0 ± 68.0</td>
</tr>
<tr>
<td>CL (liters/h)</td>
<td>222.34 (179.0–505.0)</td>
<td>470.0 (426.1–790.0)</td>
<td>1810.4 (1740.0–1876.0)</td>
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<tr>
<td>Vc (liters)</td>
<td>16.4 ± 6.3 (8.3–25.7)</td>
<td>17.5 ± 4.3 (11.5–21.2)</td>
<td>6.2 ± 3.9 (2.4–10.1)</td>
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| Mean ± SD (median; range) number of pharmacodynamic data points per subject from children administered topotecan with and without subsequent filgrastim and from NHPs administered topotecan without subsequent filgrastim were 9.3 ± 2.6 (10; 6–15), 7.9 ± 2.9 (7; 5–14), and 8.9 ± 0.7 (9.0; 8–10), respectively. The greater number (i.e., >10) of pharmacodynamic data points for some patients administered topotecan with and without filgrastim was attributable to prolonged neutropenia. However, the model fit of the data was similar for subjects with a short duration of neutropenia and few neutrophil measurements (e.g., n = 5) compared with subjects with a prolonged duration of neutropenia and a greater number of neutrophils (e.g., n > 10). In addition, patients with neutropenia lasting longer than the 21st day (i.e., 504 h after the start of treatment) of cycle 1 were delayed in receiving cycle 2. Thus, the ABC was calculated from 0 to 700 h in all patients and NHPs. A representative time course and model fit of the neutrophil survival fraction in a patient administered topotecan without subsequent filgrastim are represented in Fig. 4. A representative time course and model fit of the neutrophil survival fraction in a NHP administered topotecan without subsequent filgrastim are represented in Fig. 5. The mean ± SD model fits (i.e., R²) of the neutrophil survival fraction in children administered topotecan with and without subsequent filgrastim and in NHPs administered topotecan without filgrastim were 0.85 ± 0.08, 0.85 ± 0.18, and 0.80 ± 0.21, respectively. The MPEs for all data, for children administered topotecan with and without subsequent filgrastim, and for NHPs administered topotecan without subsequent filgrastim were −0.08 ± 0.15, −0.10 ± 0.12, −0.06 ± 0.15, and −0.07 ± 0.10, respectively. The RMSE for all data, for children administered topotecan with and without subsequent filgrastim, and for NHPs administered topotecan without filgrastim was 0.28, 0.32, 0.24, and 0.26, respectively. Residuals of prediction (predicted surviving fraction − observed surviving fraction) plotted against time for all patients after the start of topotecan are presented in Fig. 6. Negative residuals from 0 to 96 h were explained by the inherent variability in neutrophil counts at baseline and immediately after administration and by transient increases in neutrophils after topotecan administration. Negative residuals occurring ≥384 h after the start of treatment were explained by transient increases in neutrophils during recovery and an overshoot of neutrophil counts observed in some patients.

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rate constant (two-compartment model describing the systemic disposition of blood. This is similar to our model; however, in addition to the model describing the time course of leukocytes in peripheral taxel was used as input to the pharmacodynamic portion of the macokinetic model describing the systemic disposition of paclitaxel-induced neutropenia in humans. The model estimate of ABC at similar topotecan dosages and the ratio of ABC to AUCLAC depicted the differences in the severity and duration of neutropenia induced by anticancer drugs. Our model describes the time course of neutropenia and quantifies the extent and duration of neutropenia in children administered topotecan with or without subsequent filgrastim and in NHPs receiving topotecan without subsequent filgrastim. Application of this approach may provide a mathematical means to describe the differences in the severity and duration of neutropenia induced by anticancer agents. Moreover, the clinical relevance of this model is underscored by the need to correlate drug exposure of anticancer drugs and the degree and duration of neutropenia and to ideally predict which patients may be at increased risk of neutropenia-related complications (6–8, 25, 26).

Minami et al. (23) previously developed an indirect response model to describe the time course of leukopenia associated with anticancer agents in patients not receiving colony stimulating factors. In their model, a three-compartment pharmacokinetic model describing the systemic disposition of paclitaxel was used as input to the pharmacodynamic portion of the model describing the time course of leukocytes in peripheral blood. This is similar to our model; however, in addition to the two-compartment model describing the systemic disposition of topotecan, we added an additional uncoupled compartment (compartment-3) and rate constant (kₑₒ) describing the concentration of topotecan in the bone marrow and distribution of drug to and from the bone marrow, respectively. The uncoupled compartment may make our model more physiologically relevant based on the assumption that only a fraction of the drug exposed in the plasma reaches peripheral tissue, such as the bone marrow (27, 28). Pharmacokinetic modeling using uncoupled compartments to describe drug concentrations in peripheral tissues, where it is difficult to determine an accurate estimate of the tissue volume, has been used to model drug concentrations in tumors and cerebrospinal fluid (27, 28).

The basic structure of the pharmacodynamic model by Minami et al. (23) was a physiological indirect-response model. In addition, the model assumed differentiation stages of sensitivity for myeloid cells to anticancer drugs, where exposure to a drug during the sensitive period as a function of time was used to inhibit the production of leukocytes in bone marrow. Our model was modified from an indirect response model with production linked to an effect compartment (19, 21) and did not require the factor of fractional inhibition used in the model by Minami et al. (23). Minami et al. used a lag time to describe the delay between effect of paclitaxel on leukocytes in bone marrow and the measured response in the peripheral blood. The ADAPT modeling program that was used to generate our model does not allow for the incorporation of a lag time within the structure of a model; however, the use of the rate constant (kₑₒ) and delay compartment (compartment-5), modified from the delay-chain model used to describe oral absorption, produced the same effect as a lag time (22). The use of the delay chain in our pharmacodynamic model may be more physiologically relevant because the maturation and movement of neutrophils from the bone marrow to the blood is a gradual process and not an absolute time delay as would be depicted by a lag time. The measures of predictive performance (i.e., MPE and RMSE) were similar for our model and the model of Minami et al. (23). In addition, the relatively high coefficient of variation for the parameters estimated in our model were similar to those reported by Minami et al. Thus, the high interpatient variability in pharmacodynamic parameters may be a result of clinically relevant patient-specific characteristics, such as prior treatment, bone marrow reserve, and the coadministration of colony-stimulating factors.

Previous studies have used percentage decrease in neutropenia as a surrogacy for their efficacy in reducing neutropenia. The present study challenges this approach by providing a model to predict the time course of neutropenia and quantifies the extent and duration of neutropenia induced by anticancer agents. Moreover, the clinical relevance of this model is underscored by the need to correlate drug exposure of anticancer drugs and the degree and duration of neutropenia and to ideally predict which patients may be at increased risk of neutropenia-related complications (6–8, 25, 26).

Fig. 4 Representative time course of the neutrophil survival fraction in a child administered topotecan without subsequent filgrastim. The patient was administered topotecan at 1.4 mg/m²/day daily for 5 days. Individual neutrophil survival fraction points (●) and the best-fit line (—) of the data are presented.

Fig. 5 Representative time course of the neutrophil survival fraction in a NHP administered topotecan without subsequent filgrastim. The NHP was administered topotecan at 20 mg/m²/day daily for 5 days. Individual neutrophil survival fraction points (●) and the best-fit line (—) of the data are presented.
phils at the nadir and the fraction of neutrophils at nadir compared with baseline as pharmacodynamic measures of chemotherapy-induced neutropenia (13, 14, 26). However, these measures may not adequately characterize the pharmacodynamic differences between drugs and patients with regard to chemotherapy-induced neutropenia. For example, as depicted in Fig. 3, the topotecan-induced neutrophil survival fractions at nadir were similar (P > 0.05) in children administered topotecan with filgrastim (0.11 ± 0.17) and without filgrastim (0.12 ± 0.09) and in NHPs administered topotecan without filgrastim (0.09 ± 0.08). However, the time courses of neutropenia were significantly different among the groups at similar topotecan dosages (Figs. 4 and 5). The ratio of ABC to \( \text{AUC}_{\text{LAC}} \) represented the differences in sensitivities of topotecan-induced neutropenia among the groups.

There is a need to develop preclinical models of chemotherapy-induced neutropenia and to evaluate the utility of colony-stimulating factors in reducing the severity of this toxicity. NHPs are used as models for radiation-induced bone marrow suppression (10, 29, 30); however, it is unclear whether a NHP is a good model of chemotherapy-induced bone marrow suppression. The standard regimen of topotecan in the treatment of solid tumors is 1.5 mg/m²/day in adults (31, 32) and 2.0–2.4 mg/m²/day in children (11, 12), with dosages administered daily for 5 days and repeated every 21 days. Rowinsky et al. (33) achieved a maximum tolerated dosage of 4.5 mg/m²/day daily for 5 days, repeated every 21 days, in adults with refractory or relapsed acute leukemia. In a previous study using NHPs, topotecan produced very limited neutropenia (16). Thus, the starting dosage evaluated in our NHP study was 5 mg/m²/day for 5 consecutive days administered without subsequent filgrastim. The starting and two subsequent dosages (10 and 20 mg/m²/day) of topotecan administered without subsequent filgrastim did not produce significant neutropenia or thrombocytopenia in the NHPs. The resistance of NHPs to topotecan-induced neutropenia is represented by the 6.4-fold lower ratio of ABC to \( \text{AUC}_{\text{LAC}} \) in NHPs administered topotecan without subsequent filgrastim compared with children administered topotecan without subsequent filgrastim (P < 0.05).

The topotecan lactone clearances in the NHP model after administration of 5 mg/m² (30.4 ± 13.0 liters/h/m²), 10 mg/m² (23.2 ± 13.7 liters/h/m²), and 20 mg/m² (21.8 ± 9.5 liters/h/m²) are similar to those reported in the POG study (16.7 ± 6.5 liters/h/m²), from which we analyzed the absolute neutrophil
AUCLAC to AUC TOT in the NHP model is similar to those ministered as a 30-min infusion (12, 34). In addition, the ratio of marrow to the peripheral blood. The statistical difference in or to a delay in maturity or movement of cells from the bone cond, the similar (reported in the POG and St. Jude studies (12, 34). Thus, the
istered topotecan with and without filgrastim and in NHPs related to inhibition of stem cells. Erickson-Miller
istered topotecan with and without filgrastim suggests that the sensitivity difference is
ation of neutropenia. Future studies will validate our pharmacokinetic-pharmacodynamic model in patients receiving standard dosages of topotecan and in patients receiving dosages of 7.5 mg/m²/day as part of bone marrow transplant regimens. In addition, future prospective studies are required to determine the relationship between ABC and clinically significant outcomes such as neutropenic fever.

REFERENCES
