Carboplatin (cis-diammine-1,1-cyclobutanedicarboxylate platinum [II]) is active against a wide variety of carcinomas and sarcomas in cats. The dose-limiting toxicosis associated with carboplatin administration in cats is neutropenia. Determination of carboplatin dose on the basis of BSA consistently predicts the severity of drug-associated neutropenia in healthy young cats but not in older tumor-bearing cats.

Phase I evaluation of carboplatin by use of a dosing strategy based on a targeted area under the platinum concentration-versus-time curve and individual glomerular filtration rate in cats with tumors

Dennis B. Bailey, DVM; Kenneth M. Rassnick, DVM; Nathan L. Dykes, DVM; Lakshmi Pendyala, PhD

Objective—To determine whether a carboplatin dose calculation that is based on a targeted area under the concentration-versus-time curve (AUC_target) and individual glomerular filtration rate (GFR) accurately predicts carboplatin-associated myelotoxicoses in tumor-bearing cats, and to determine the maximum tolerated AUC_target.

Animals—32 cats with tumors.

Procedures—in each cat, plasma clearance of technetium Tc 99m-labeled diethylenetriaminepentaacetic acid was measured to assess GFR. Carboplatin was administered IV. The dose was calculated by use of an equation as follows: Dose = AUC_target × 2.6 × GFR × body weight. Initial AUC_target was 2.0 min•mg•mL⁻¹ and was increased in increments of 0.50 min•mg•mL⁻¹ in cohorts of 3 cats. To assess myelotoxic effects, CBCs were performed weekly for ≥ 4 weeks. Following identification of the maximum tolerated AUC_target, additional cats were treated at that AUC_target and plasma platinum concentrations were measured in 6 cats.

Results—The AUC_target values ranged from 2.0 to 3.0 min•mg•mL⁻¹. Neutropenia was the dose-limiting toxicosis, and the maximum tolerated AUC_target was 2.75 min•mg•mL⁻¹. Nineteen cats received this dose of carboplatin; 13 became neutropenic, but only 1 developed severe neutropenia (< 500 neutrophils/µL), and none had neutropenia-associated clinical signs. In the cats that had plasma platinum concentration determined, the difference between AUC_target and the measured value ranged from –0.23 to 0.31 min•mg•mL⁻¹ (median, 0.20 min•mg•mL⁻¹).

Conclusions and Clinical Relevance—in cats, carboplatin-associated myelotoxicoses were accurately and uniformly predicted by use of the proposed dosing strategy. The maximum tolerated AUC_target for a single dose of carboplatin was 2.75 min•mg•mL⁻¹. (Am J Vet Res 2009;70:770–776)
function because $\text{Cl}_b$ in cats is directly proportional to GFR. Chronic renal insufficiency and chronic renal failure are much more common in older cats. Consequently, the ranges of GFR and $\text{Cl}_b$ among older tumor-bearing cats would be expected to be wide. Nonrenal plasma clearance, which occurs primarily via tissue binding, is minimal in cats.

The AUC is strongly predictive of the severity of carboplatin-associated neutropenia in cats. The dose of any given drug needed to achieve a given targeted AUC is predicted by the following equation:

$$\text{Dose} = \text{AUC} \times \text{clearance}$$

For an individual cat, $\text{Cl}_b$ can be estimated from the cat's GFR and weight. On the basis of such information, we previously derived an equation to determine carboplatin dose that was based on $\text{AUC}_{\text{target}}$, patient GFR, and patient BW$_{\text{kg}}$:

$$\text{Carboplatin dose} = \text{AUC}_{\text{target}} \times 2.6 \times \text{GFR} \times \text{BW}_{\text{kg}}$$

The objective of the study reported here was to evaluate the dose equation prospectively in tumor-bearing cats to confirm that it enabled accurate prediction of the severity of carboplatin-associated neutropenia and to define the maximum tolerated $\text{AUC}_{\text{target}}$. An additional objective was to determine how closely $\text{AUC}_{\text{target}}$ correlated with AUC values calculated from serial measurements of plasma platinum concentrations.

**Materials and Methods**

**Cats**—Client-owned cats with histologically confirmed solid tumors were used in the study. Cats with tumors that had been surgically excised were eligible for inclusion, but cats that received any previous chemotherapeutic drugs or radiation therapy were excluded. Concurrent illnesses, including any that potentially could affect GFR (eg, renal insufficiency or hyperthyroidism), did not preclude inclusion in the study. All owners provided written informed consent, and the study design was approved by the Cornell University Institutional Animal Care and Use Committee.

After completing their involvement in the study, cats continued to receive treatment with carboplatin if indicated or other treatments were provided, including surgery, radiation therapy, and administration of other chemotherapeutic agents.

**Measurement of GFR**—For each cat, a baseline CBC, serum biochemical analyses, and urinalysis were performed; within the following 7-day period (usually within 1 day), GFR was estimated by measurement of plasma clearance of $^{99m}\text{Tc-DTPA}$. Briefly, an approximately 1-mCi dose of $^{99m}\text{Tc-DTPA}$ was injected (0 minutes) as an IV bolus via a peripheral catheter placed in a cephalic vein. Blood samples (1.5 mL each) were collected from a sampling catheter placed in a jugular or medial saphenous vein into tubes containing EDTA at 15, 30, 60, 150, and 240 minutes after isotope injection. Within 2 hours after the last blood sample was collected, plasma radioactivity was counted in all tubes by use of a sodium iodide well counter. The samples then were fit to a 1-compartment monoeponential model, and AUC was calculated as $C_0/k$, where $C_0$ was the extrapolated radioactivity at zero time and $k$ was the elimination constant (slope) of the decay curve. Plasma clearance of $^{99m}\text{Tc-DTPA}$ was calculated by dividing the injected dose by AUC and BW$_{\text{kg}}$. All calculations were performed by use of a computer software program.

**Carboplatin administration**—Each cat received a single dose of carboplatin the day after GFR measurement was performed. Carboplatin was administered as an IV bolus via a cephalic or medial saphenous vein, and the dose was calculated by use of a previously derived formula as follows:

$$\text{Dose} = \text{AUC}_{\text{target}} \times 2.6 \times \text{GFR} \times \text{BW}_{\text{kg}}$$

The initial $\text{AUC}_{\text{target}}$ was set at 2.0 min$^{-1}$mg$^{-1}$L on the basis of results of a previous study by our group; in that study, there was minimal to no myelosuppression in any cats in which the measured carboplatin AUC was $\leq 2.0$ min$^{-1}$mg$^{-1}$L. Increases in $\text{AUC}_{\text{target}}$ were evaluated in cohorts of 3 cats. If none of the 3 treated cats in a given cohort developed unacceptable toxic effects, the $\text{AUC}_{\text{target}}$ for the next cohort was increased by 0.5 min$^{-1}$mg$^{-1}$L. If one of the cats developed unacceptable toxicosis, an additional 3 cats were treated at that $\text{AUC}_{\text{target}}$; if no additional cats developed unacceptable toxic effects at that $\text{AUC}_{\text{target}}$, the dose escalation experiment was continued. If $\geq 2$ cats in a cohort developed unacceptable toxic effects, the $\text{AUC}_{\text{target}}$ was subsequently decreased by 0.25 min$^{-1}$mg$^{-1}$L. The maximum tolerated $\text{AUC}_{\text{target}}$ was defined as the maximum $\text{AUC}_{\text{target}}$ at which $\leq 1$ of 6 cats developed unacceptable toxicosis. Once the maximum tolerated $\text{AUC}_{\text{target}}$ was established, additional cats were treated with carboplatin at that $\text{AUC}_{\text{target}}$ to further characterize any associated toxicoses.

Although the carboplatin dose was calculated by use of the aforementioned equation, an equivalent dose based on BSA (mg/m$^2$) was also calculated for each cat. Body surface area was estimated by use of a formula as follows:

$$\text{BSA} = \frac{\text{body weight in grams}^{0.425} \times 1,000}{\text{height in centimeters}^{0.725}}$$

**Evaluation of toxic effects**—For each cat, CBCs were performed weekly for a minimum of 4 weeks after treatment with carboplatin (day 0). If the neutrophil or platelet count was not within reference limits by the fourth week, weekly CBCs were continued until the values were within reference limits. Serum biochemical analyses and urinalysis were repeated at the fourth week. Adverse gastrointestinal tract effects were assessed by owners and reported at weekly recheck examinations. All toxicoses were graded by established criteria set forth by the Veterinary Co-operative Oncology Group (Appendix).

Unacceptable toxicosis was defined as either nonclinical grade 4 neutropenia; febrile neutropenia; grade 4 thrombocytopenia; $\geq$ grade 3 anorexia, vomiting, or diarrhea; or death.

**Pharmacokinetic analysis**—Once the dose escalation experiment was completed and the maximum tol-
erated AUC\textsubscript{\textit{target}} was established, pharmacokinetic analysis was performed in 6 cats treated at this AUC\textsubscript{\textit{target}}. Baseline evaluation for these cats was performed as previously described. In addition, a blood sample (1.5 mL) was collected into a tube containing heparin immediately prior to carboplatin administration. The carboplatin dose then was administered (0 minutes) rapidly as an IV bolus through the peripheral catheter that was used for the GFR study, and blood samples were collected from the sampling catheter that was used for the GFR study into heparinized tubes at 15, 30, 60, 90, 120, 240, and 480 minutes after carboplatin administration. These were the same collection time points as those used previously for determination of the carboplatin dosing equation.\textsuperscript{a} All blood samples were centrifuged immediately; the plasma was separated and stored at −70°C until the platinum assay was performed.

Plasma platinum concentration was measured by use of an atomic absorption spectrophotometer with a platform graphite furnace equipped with an autosampler and accompanying computer software. Plasma was diluted (10×) in a diluent that consisted of 0.2% nitric acid and 0.1% Triton X-100. Samples were analyzed by use of 20-μL aliquots. The analytic standards were prepared in plasma that was similarly diluted. The standard curve range was 25 to 800 ng/mL. The graphite furnace program consisted of drying at 130°C and 150°C, pyrolysis at 1,400°C, atomization at 2,200°C, and clean out at 2,400°C. Quality control samples were analyzed at the beginning and end of each analysis to ensure assay integrity. Plasma platinum AUC was calculated for each cat by use of the trapezoidal rule with no correction for the period from the final time point to infinity.

**Statistical analysis**—A Kruskal-Wallis 1-way ANOVA was performed to determine whether there was a difference in absolute neutrophil count nadir among the AUC\textsubscript{\textit{target}} cohorts. If an overall difference was identified, a Dunn multiple comparison was used to identify differences among the individual cohorts. Additionally, a χ\textsuperscript{2} test was used to determine whether there was a difference in the frequency of neutropenia or the frequency of unacceptable toxicoses among the AUC\textsubscript{\textit{target}} cohorts.

Spearman rank correlation was used to determine whether the absolute neutrophil count at the nadir was inversely correlated with the equivalent dose that was based on BSA. A similar correlation analysis to evaluate the relationship between absolute neutrophil count nadir and AUC\textsubscript{\textit{target}} was performed because the cats were assigned to few AUC\textsubscript{\textit{target}} values; therefore, the assumptions for correlation analysis were not met.\textsuperscript{15} For the cats that were treated at the maximally tolerated AUC\textsubscript{\textit{target}} and had plasma platinum concentrations measured, AUC\textsubscript{\textit{target}} and the measured AUC were compared by use of summary statistics.

For all statistical tests, a value of \( P < 0.05 \) was considered significant. All statistical calculations were performed by use of a computer software program.\textsuperscript{4}

**Results**

Thirty-two cats were enrolled in the study between December 2003 and December 2007. Breeds included domestic shorthair (\( n = 21 \)), domestic longhair (7), Siamese (2), Maine Coon (1), and Persian (1). There were 17 castrated males and 15 spayed females. Median age was 13 years (range, 3 to 17 years); 23 cats were ≥ 10 years of age. Eighteen cats had carcinomas; these included oral carcinomas (\( n = 6 \)), hepatobiliary carcinoma (3), mammary adenocarcinoma (2), basosquamous cutaneous carcinoma (2), eccrine sweat gland carcinoma (1), salivary adenocarcinoma (1), small intestinal carcinoma (1), colonic carcinoma (1), and pulmonary carcinoma (1). Fourteen cats had soft tissue sarcomas; these included fibrosarcoma (\( n = 10 \)), myxofibrosarcoma (1), malignant fibrous histiocytoma (1), cutaneous hemangiosarcoma (1), and intra-abdominal extraskelatal chondrosarcoma (1).

Twenty-four cats had baseline neutrophil counts that were within the reference range, and 8 had high counts (overall range, 3,000 to 30,500 neutrophils/μL; reference range, 2,300 to 11,000 neutrophils/μL). Two cats had baseline platelet counts that were below the lower limit of the reference range, 29 had platelet counts within reference range, and 1 had a high count (overall range, 157,000 to 707,000 platelets/μL; reference range, 195,000 to 624,000 platelets/μL).

On the basis of results of the baseline serum biochemical analyses and urinalysis, 6 cats had renal insufficiency that was characterized by azotemia and inadequately concentrated urine. Five of those cats had high serum creatinine concentration (range for all 6 cats, 2.0 to 3.3 mg/dL; reference range, 0.7 to 2.3 mg/dL). Four of the 6 cats had high SUN concentration (range for all 6 cats, 28 to 74 mg/dL; reference range, 17 to 35 mg/dL). Urine specific gravity ranged from 1.014 to 1.022 among the 6 cats. The cat in which serum creatinine concentration was slightly less than the upper limit of the reference range (2.0 mg/dL) had a history of renal insufficiency, was polyuric and polydipsic, had high SUN concentration (41 mg/dL), and had poorly concentrated urine (urine specific gravity, 1.014). Additionally, nonrenal causes for the high SUN concentration were not identified in this cat.

The overall median GFR for all 32 cats was 1.93 mL/min×kg\textsuperscript{−1} (range, 0.85 to 2.91 mL/min×kg\textsuperscript{−1}). The median GFR for the cats with clinically normal renal function was 2.01 mL/min×kg\textsuperscript{−1} (range, 1.26 to 2.91 mL/min×kg\textsuperscript{−1}). In contrast, the median GFR for the 6 cats with clinical renal insufficiency was 1.04 mL/min×kg\textsuperscript{−1} (range, 0.85 to 1.79 mL/min×kg\textsuperscript{−1}); 4 of those cats had GFR values that were less than any value among the cats with clinically normal renal function.

After a single treatment with carboplatin, 5 cats developed nonclinical grade 1 or 2 thrombocytopenia. Adverse gastrointestinal tract effects also were uncommon. Four cats developed grade 1 anorexia, and 1 cat developed grade 2 anorexia. Vomiting and diarrhea were not reported for any of the cats.

Neutropenia was the principal toxic effect associated with carboplatin among the 32 cats. None of the 3 cats that were treated at an AUC\textsubscript{\textit{target}} of 2.0 mg×min×kg\textsuperscript{−1} became neutropenic (Figure 1; Table 1). Only the 3 cats that were treated at an AUC\textsubscript{\textit{target}} of 2.5 mg×min×kg\textsuperscript{−1} developed grade 2 neutropenia. The neutrophil count nadir was measured at day 21, and the neutrophil count...
AUC was within reference limits at day 35. Seven cats were treated at an AUC\textsubscript{target} of 3.0 min\textsuperscript{-1}mg\textsuperscript{mL-1}. An additional cat was enrolled in this cohort because complete information regarding toxic effects of carboplatin was not yet available from the sixth cat when the seventh was enrolled. Six of the 7 cats became neutropenic; of these, 2 developed grade 1 neutropenia, 1 developed grade 2 neutropenia, 2 developed grade 3 neutropenia, and 1 developed grade 4 neutropenia. Neutrophil count nadirs were identified at day 14 (n = 3 cats) or day 21 (3). Neutrophil counts for all of the cats with grade 1 or 2 neutropenia were within reference limits at day 28, regardless of whether the nadir was detected on day 14 or 21. Of the 3 cats with grade 3 or 4 neutropenia, neutrophil counts in 2 were not within reference limits until day 35. The third cat developed grade 3 neutropenia (564 neutrophils/µL) on day 14 and that same day became hypothermic (rectal temperature, 37.5°C), anorexic, and lethargic. There was no improvement with supportive care, and the cat was euthanatized 3 days later. Subsequently, the AUC\textsubscript{target} for the next cohort was decreased to 2.75 min\textsuperscript{-1}mg\textsuperscript{mL-1}. Initially, 6 cats were enrolled in that cohort; after treatment, grade 1 neutropenia was identified in 2 of the cats. On the basis of this finding, the maximum tolerated AUC\textsubscript{target} was determined to be 2.75 min\textsuperscript{-1}mg\textsuperscript{mL-1}. Additional cats then were enrolled in this cohort; overall, 19 cats were treated at this AUC\textsubscript{target}. Eight cats developed grade 1 neutropenia, 1 cat developed grade 2 neutropenia, 3 cats developed grade 3 neutropenia, and 1 cat developed grade 4 neutropenia. The neutrophil count nadir was identified at day 7 in 1 cat, at day 14 in 9 cats, at day 21 in 7 cats, and at day 28 in 2 cats. At day 28, the neutrophil count was within reference limits in 16 cats; in the remaining 3 cats, the neutrophil count was within reference limits at day 35. None of the cats in this cohort had neutropenia-associated clinical signs.

Because of the small numbers of cats enrolled in both the 2.0 and 2.5 min\textsuperscript{-1}mg\textsuperscript{mL-1} cohorts, the data obtained from the cats in these 2 cohorts were combined for analysis of the relationship between AUC\textsubscript{target} and neutropenia. Absolute neutrophil count nadirs were measured, the median carboplatin dose for the 19 cats treated at the maximum tolerated AUC\textsubscript{target} was 227 mg/m\textsuperscript{2} (range, 89 to 295 mg/m\textsuperscript{2}); Figure 2). From this data obtained for all 32 cats, the equivalent carboplatin dose (based on BSA) was inversely correlated with absolute neutrophil count nadir (r = –0.47; P = 0.007). The coefficient of determination \( r^2 \) was 0.22.

For the 6 cats treated at the maximum tolerated AUC\textsubscript{target} of 2.75 min\textsuperscript{-1}mg\textsuperscript{mL-1} in which plasma platinum concentrations were measured, the median calculated AUC was 2.95 min\textsuperscript{-1}mg\textsuperscript{mL-1} (range, 2.32 to 3.06 min\textsuperscript{-1}mg\textsuperscript{mL-1}). Calculated AUC was less than the AUC\textsubscript{target} in 1 cat and greater than the AUC\textsubscript{target} in 5 cats.

<table>
<thead>
<tr>
<th>Targeted AUC (min\textsuperscript{-1}mg\textsuperscript{mL-1})</th>
<th>No. of cats</th>
<th>Grade of neutropenia*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.00</td>
<td>3</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>2.50</td>
<td>3</td>
<td>0 2 0 0 0</td>
</tr>
<tr>
<td>2.75</td>
<td>19</td>
<td>6 8 1 3 1</td>
</tr>
<tr>
<td>3.00</td>
<td>7</td>
<td>1 2 1 2 1</td>
</tr>
</tbody>
</table>

*Neutropenia was graded as follows: grade 0, ≥ 2,500 neutrophils/µL; grade 1, 1,500–2,499 neutrophils/µL; grade 2, 1,000–1,499 neutrophils/µL; grade 3, 500–999 neutrophils/µL; and grade 4, < 500 neutrophils/µL.

Figure 1.—Values of absolute neutrophil count nadir in 32 cats with solid tumors that received a single carboplatin treatment IV at targeted AUCs of 2.00 (n = 3), 2.50 (3), 2.75 (19), and 3.00 (7) min\textsuperscript{-1}mg\textsuperscript{mL-1}. The solid line identifies the lower limit of the neutrophil count reference range (2,300 cells/µL) and the dashed line identifies the lower limit of acceptable neutropenia with no clinical signs (500 cells/µL) in cats.

Figure 2.—Correlation between absolute neutrophil count nadir and equivalent carboplatin dose (based on BSA) for the same 32 cats included in Figure 1. The equivalent carboplatin dose was inversely correlated with absolute neutrophil count nadir (r = –0.47; P = 0.007). See Figure 1 for key.
The median absolute difference between calculated and targeted AUC was 0.20 min\(\text{mg}\cdot\text{mL}^{-1}\) (range, −0.23 to 0.31 min\(\text{mg}\cdot\text{mL}^{-1}\)). One of these cats did not develop neutropenia; 4 cats developed grade 1 neutropenia, and 1 cat developed grade 3 neutropenia.

**Discussion**

Historically, carboplatin, like many chemotherapeutic drugs, has been administered to cats in doses that are derived from estimated patient BSA.\(^1\)\(^2\)\(^3\)\(^4\)\(^5\) This convention is based on the assumption that BSA reflects drug distribution, metabolism, and excretion.\(^6\) However, dose calculation on the basis of estimated BSA does not accurately predict the severity of carboplatin-associated neutropenia in cats. In a recently published phase I dose escalation study,\(^6\) carboplatin was administered to 64 tumor-bearing cats at doses ranging from 180 to 260 mg/m\(^2\). Hematologic toxic effects were assessed in 48 of those cats. Only 1 cat developed grade 4 neutropenia after treatment with an equivalent dose (based on BSA) of 220 mg/m\(^2\). Additionally, in that study, the relative frequencies with which neutropenia \(\geq\) grade 3 developed were similar in cats treated with equivalent doses of 200 mg/m\(^2\) (20%), 220 mg/m\(^2\) (17%), 240 mg/m\(^2\) (33%), and 260 mg/m\(^2\) (22%). Similarly, in the present study, the correlation between equivalent dose (based on BSA) and absolute neutrophil count nadir was weak; the coefficient of determination \((r^2)\) was 0.22, indicating that only 22% of the variation in absolute neutrophil count nadir could be accounted for by dose calculation on the basis of BSA.

In contrast, the dose-response relationship was much more clearly defined by use of the dosing strategy evaluated in the present study. Significant differences were identified among the AUC\(_{\text{Target}}\) cohorts with respect to absolute neutrophil count nadir, the frequency of development of carboplatin-associated neutropenia, and the frequency of development of unacceptable toxic effects. Also, for the purposes of informal comparison of data from the present study and findings of the previous investigation,\(^6\) the relative frequencies with which neutropenia \(\geq\) grade 3 developed in cats treated with equivalent doses of 200 mg/m\(^2\) (20%), 220 mg/m\(^2\) (17%), 240 mg/m\(^2\) (33%), and 260 mg/m\(^2\) (22%). Similarly, in the present study, the correlation between equivalent dose (based on BSA) and absolute neutrophil count nadir was weak; the coefficient of determination \((r^2)\) was 0.22, indicating that only 22% of the variation in absolute neutrophil count nadir could be accounted for by dose calculation on the basis of BSA.

The maximum tolerated AUC\(_{\text{Target}}\) identified in the present study was 2.75 min\(\text{mg}\cdot\text{mL}^{-1}\). Of the 19 cats that were treated at this AUC\(_{\text{Target}}\), 13 developed some form of neutropenia and most of the cats that did not develop neutropenia had neutrophil count nadirs that were near the lower limit of the reference range. The high incidence of neutropenia indicated that for most cats, the carboplatin dose calculated by use of the dosing strategy was close to the maximum dose that can be administered safely. However, it is equally important that only 1 of the 19 cats treated with this dose of carboplatin developed grade 4 neutropenia, and none of the cats had neutropenia-associated clinical signs. Therefore, although some toxic effect on neutrophils was evident consistently, the severity of the toxic effect was well within acceptable limits for clinical cancer treatments in veterinary patients.\(^6\)\(^7\)\(^8\) In contrast, when treatment at an AUC\(_{\text{Target}}\) of 3.0 min\(\text{mg}\cdot\text{mL}^{-1}\) was evaluated, the proportion of cats with unacceptable toxicities increased to 2 of 7 cats (grade 4 neutropenia in 1 cat and clinically apparent grade 3 neutropenia and death in another), which illustrates the steepness of the dose-response curve for carboplatin-associated toxicosis when this dosing strategy is used.

Data collected from the 6 cats in which plasma platinum concentrations were measured revealed good agreement between the calculated and targeted AUC. On the basis of a median difference of 0.20 min\(\text{mg}\cdot\text{mL}^{-1}\), the AUC\(_{\text{Target}}\) underestimated the calculated AUC by a median of 7%, which was well within the 20% error identified when a similar dosing strategy was evaluated in humans.\(^9\)\(^10\) Therefore, these data suggest that no modification to the dosing equation is indicated. However, it is interesting that the median calculated AUC was 2.95 min\(\text{mg}\cdot\text{mL}^{-1}\), and the AUC\(_{\text{Target}}\) calculated of 3.0 min\(\text{mg}\cdot\text{mL}^{-1}\) was associated with unacceptable and clinically apparent toxic effects. Plasma platinum concentrations were not measured in cats in the 3.0 min\(\text{mg}\cdot\text{mL}^{-1}\) cohort. Thus, it cannot be determined whether the calculated AUC values for cats in that cohort would have overlapped with calculated values for the cats enrolled in the 2.75 min\(\text{mg}\cdot\text{mL}^{-1}\) cohort or whether the latter would have been similarly increased relative to the corresponding AUC\(_{\text{Target}}\). Complete pharmacokinetic analysis of total plasma platinum (free and protein-bound) following administration of carboplatin to tumor-bearing cats has been described elsewhere.\(^4\)

The AUC is the pharmacokinetic parameter that most accurately predicts carboplatin-associated toxicoses in humans and cats.\(^3\)\(^11\)\(^12\) The AUC is directly proportional to dose and inversely proportional to clearance.\(^6\) Carboplatin clearance can be accurately predicted from patient GFR because the drug is eliminated primarily by the kidneys. As much as 80% and 90% of the platinum dose is eliminated in the urine within 4 hours after administration of carboplatin to people and mice, respectively.\(^7\)\(^12\) In Beagles, as much as 85% of the platinum is excreted in the urine within 96 hours after administration of carboplatin, and most is eliminated within the first 24 hours.\(^13\) Urinary excretion of carboplatin has not been thoroughly evaluated in cats, to our knowledge, but carboplatin likely is eliminated primarily by the kidneys in this species because \(C_{\text{pl}}\) can be estimated from patient GFR.\(^4\)

For a given carboplatin dose, AUC and toxic effects increase as GFR and carboplatin clearance decrease. This is illustrated by multiple examples where carboplatin-associated toxicosis was more severe in individuals with impaired renal function, both humans and a dog.\(^2\)\(^14\)\(^15\)\(^16\)\(^17\)\(^18\)\(^19\) Additionally, in a previous study\(^4\) by our group in which carboplatin dose was not adjusted to account for patient renal function, cats with lower GFR measurements developed more severe neutropenia after treatment with the drug. The prevalence of chronic renal insufficiency and chronic renal failure is high among older tumor-bearing cats. Combining the results of 2 studies\(^6\)\(^10\) in which a total of 14 healthy adult cats with no evidence of renal disease were evaluated, GFR measurements that were based on plasma clearance of \(^99\)Tc-DTPA ranged from 1.71 to 4.19 mL\(\text{min}^{-1}\)\(\text{kg}^{-1}\) in the present study, 11 of 32 (34%) tumor-bearing cats...
had GFR measurements < 1.71 ml·min⁻¹·kg⁻¹. Only 6 (19%) cats had clinical evidence of chronic renal insufficiency or chronic renal failure, which emphasizes the usefulness of the dosing strategy used in the present study for all cats that require treatment with carboplatin and not just for those with known renal impairment.

An important limitation of the dosing scheme used in the present study is the lack of a simple, readily available technique to measure GFR. Inulin clearance or exogenous creatinine clearance measurements are considered to be the gold standard, but these procedures are labor intensive and require general anesthesia of patients for urinary catheter placement. We chose to measure plasma clearance of ⁹⁹ᵐTc-DTPA because it is an accurate technique and because it is much less technically demanding than the aforementioned clearance measurements, given that only serial blood samples need to be collected. However, few veterinary hospitals currently provide nuclear medicine services. Assessment of plasma clearance of iohekol is an accurate method for GFR estimation. Historically, high-performance liquid chromatography or x-ray fluorescence assays used to detect iohekol in plasma samples were not widely available, but a high-performance liquid chromatography–based assay recently became commercially available for use in dogs and cats. In contrast, plasma clearance of creatinine after a single IV injection (100 mg/kg) was not an accurate indicator of GFR in cats.

Glo meral filtration rate measurement techniques differ not only with respect to the substrate used but also with respect to the collection time points and clearance calculations. It is important to recognize that although different techniques might provide relatively similar results, they are not necessarily interchangeable. The carboplatin dosing equation used in our study has been validated for use in cats only when GFR is assessed via the ⁹⁹ᵐTc-DTPA clearance protocol described in this report. Substituting other protocols for GFR estimation might or might not necessitate modification of the dosing equation or the maximum tolerated AUC<sub>τ paranoid. Therefore, if a different GFR measurement protocol is used, it is recommended that the dosing equation and maximum tolerated AUC<sub>τ paranoid are revalidated. Fortunately, once a patient’s GFR has been measured, it is unlikely that additional GFR measurements will be needed even if that patient is scheduled to receive multiple carboplatin treatments. In people with or without abnormal renal function, no changes in GFR were detected after 1 to 6 carboplatin treatments. Also, changes in hydration status or administration of fluids IV or SC should have a minimal and clinically unimportant impact on GFR. In healthy cats, diuresis induced via infusion of saline (0.9% NaCl) solution (6 mL/kg/h) with or without mannitol did not significantly alter GFR measurements determined via assessment of inulin clearance or plasma ⁹⁹ᵐTc-DTPA clearance.

For a given individual, it is assumed that the dose-response curve representing the anti-tumor benefit of a drug usually is steep, indicating that small changes in drug dose can have dramatic effects on outcome. The serious consequences of ineffective cancer treatments make it imperative that patients be treated not just with any safe dose but rather with the maximum safe dose that can be tolerated. The results of the study of this report indicated that carboplatin-associated neutropenia was predicted accurately and consistently in cats by use of a dosing strategy that was based on a targeted plasma platinum AUC and the individual cat’s GFR, and that the maximum tolerated AUC<sub>τ paranoid was 2.75 min·mg·mL⁻¹. It is recommended that this dose prescription strategy be used for subsequent phase II clinical trials to evaluate carboplatin efficacy in cats with solid tumors.

References


Appendix

System used for grading adverse effects in tumor-bearing cats that received a single carboplatin treatment IV (based on published criteria19).

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade</th>
<th>Criterion</th>
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</tr>
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<td>3</td>
<td>15,000–49,999 platelets/µL</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>&lt; 15,000 platelets/µL</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Coaxing or dietary change required to maintain appetite</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Anorexia of &lt; 3 days’ duration; no notable weight loss</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Anorexia of 3 to 5 days’ duration; weight loss and nutritional supplements needed</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Anorexia of &gt; 5 days’ duration; life-threatening consequences</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Death</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>&lt; 3 episodes in 24 hours</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3 to 5 episodes in 24 hours; &lt; 3 episodes/d for 2 to 5 days, or SC or IV administration of fluids for &lt; 24 hours</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>&gt; 5 episodes in 24 hours; vomiting of &gt; 4 days’ duration, or IV administration of fluids for ≥ 24 hours</td>
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<tr>
<td></td>
<td>4</td>
<td>Life-threatening (eg, hemodynamic collapse)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Death</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Increase of 1 defection/d, compared with pretreatment baseline value</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Increase of 2 to 6 defections/d, compared with pretreatment baseline value, or SC or IV administration of fluids for &lt; 24 hours</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Increase of ≥ 7 defections/d, compared with pretreatment baseline value; incontinence, or IV administration of fluids for ≥ 24 hours</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Life-threatening (eg, hemodynamic collapse)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>