Evaluation of cisplatin combined with piroxicam for the treatment of oral malignant melanoma and oral squamous cell carcinoma in dogs

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Objective—To determine the maximum tolerated dose (MTD) of cisplatin administered with piroxicam, the antitumor activity and toxicity of cisplatin combined with piroxicam in dogs with oral malignant melanoma (OMM) and oral squamous cell carcinoma (SCC), and the effects of piroxicam on the pharmacokinetics of cisplatin in dogs with tumors.

Design—Prospective nonrandomized clinical trial.

Animals—25 dogs.

Procedure—Dogs were treated with a combination of cisplatin (escalating dose with 6 hours of diuresis with saline [0.9% NaCl] solution) and piroxicam (0.3 mg/kg [0.14 mg/lb], PO, q 24 h). The initial cisplatin dose (50 mg/m^2) was increased by 5 mg/m^2 until the MTD was reached. Tumor stage and size were determined at 6-week intervals during treatment. The pharmacokinetics of cisplatin were determined in dogs receiving a combination of cisplatin and piroxicam during the clinical trial and dogs that were treated with cisplatin alone.

Results—11 dogs with OMM and 9 dogs with SCC were included in the clinical trial. The MTD of cisplatin when administered in combination with piroxicam was 50 mg/m^2. Tumor remission occurred in 5 of 9 dogs with SCC and 2 of 11 dogs with OMM. The most common abnormality observed was renal toxicosis. Clearance of cisplatin in dogs that were treated with cisplatin alone was not significantly different from that in dogs treated with a combination of cisplatin and piroxicam.

Conclusions and Clinical Relevance—Cisplatin administered in combination with piroxicam had antitumor activity against OMM and SCC. The level of toxicity was acceptable, although renal function must be monitored carefully. (*J Am Vet Med Assoc* 2004;224:388–394)

Oral malignant melanoma (OMM) and oral **squamous cell carcinoma (SCC)** are the most common oral tumors in dogs. They account for 30% and 20%, respectively, of all oral neoplasia.[1] The treatment of choice for rostrally located tumors is radical surgery, radiation, or a combination of surgery and radiation.[1] The role of chemotherapy in oral tumors has not been defined. Limited information regarding the use of medical treatment for OMM and SCC is available; however, study results have been disappointing.[2-9]

Cisplatin is a broad-spectrum anticancer chemotherapeutic agent that has antitumor activity against OMM and SCC in dogs.[5,a] After administration of cisplatin, the majority of the drug is bound to plasma proteins, with the small unbound (free) fraction being responsible for the drug's anticancer activity.[10] For cisplatin to become active, it requires an environment of low chloride concentration, such as the intracellular fluid space.[10] The protein-bound portion of cisplatin cannot enter into this space. Cisplatin is cleared from the body via the kidneys. The majority is excreted in the glomerular filtrate; however, in dogs and humans there is also additional tubular secretion of cisplatin.[11] The major dose-limiting toxicities of cisplatin are nephrotoxicity, myelosuppression, and gastrointestinal toxicity.[10,11] Free cisplatin is associated, at least in part, with these toxicities.[11]

Piroxicam is a nonsteroidal anti-inflammatory drug that has antitumor activity in several types of tumors in dogs and humans.[2,9,12] In a previous phase I clinical trial,[9] piroxicam induced remission in 2 of 4 dogs with SCC. Results of another study[2] indicate that piroxicam induced remission in 3 of 17 dogs with SCC. Piroxicam has also induced remission in dogs with OMM.[b]

Synergistic antitumor activity between cisplatin and piroxicam was detected in a phase III clinical trial[13] in transitional cell carcinoma in dogs. In that study, renal toxicosis was frequent and dose-limiting, resulting in the discontinuation of cisplatin. Concurrent urinary tract disease (chronic pyelonephritis or cystitis, ureteral and urethral obstruction, hydronephrosis, and tumor invasion) in dogs with cancer of the urinary bladder may have enhanced the renal toxicity of the combination of cisplatin and piroxicam. In the study presented here, we hypothesized that the antitumor activity of piroxicam in combination with cisplatin may not be limited to transitional cell carcinoma and may be less toxic in dogs without urinary tract cancer.

The mechanisms of toxicity and enhanced efficacy

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of the combination of cisplatin and piroxicam are not known. In general, the potential causes of the renal toxicosis include direct cisplatin tubular damage combined with alterations of renal hemodynamics leading to a decrease in glomerular filtration, alteration in cisplatin protein binding, alteration of intracellular handling, and repair of cisplatin-induced damage.[12] Piroxicam could contribute to renal toxicity caused by cisplatin through effects on renal blood flow. Piroxicam may also alter the pharmacokinetics of cisplatin. If the mechanisms of the toxicity of cisplatin and piroxicam could be determined, then strategies could be developed to offset the toxicity while preserving the antitumor effects.

The purpose of the study reported here was to determine the **maximum tolerated dose (MTD)** of cisplatin administered in combination with piroxicam, the antitumor activity and toxicity of cisplatin combined with piroxicam in dogs with OMM and SCC, and the effects of piroxicam on the pharmacokinetics of cisplatin in dogs with tumors.

Materials and Methods

Clinical trial design—This study was approved by the Purdue Animal Care and Use Committee. A phase I and II clinical trial of cisplatin administered in increasing doses combined with piroxicam administered at a constant dose was performed in dogs with nonresectable OMM and SCC. Criteria for inclusion in the study included histologic confirmation of OMM or SCC, measurable tumor size, no prior treatment with cisplatin or piroxicam, initial serum creatinine and BUN concentrations that were within reference ranges, and informed consent from the owner.

Dogs were evaluated at the Purdue University Veterinary Teaching Hospital before and at 6-week intervals during treatment, until progressive disease. Evaluation included physical examination, measurement of the tumor, and thoracic (left lateral, right lateral, and ventrodorsal) and skull radiography as needed to determine disease progression. The tumor stage was determined and recorded according to the World Health Organization TNM classification.[14]

A CBC, platelet count, serum biochemical analyses, and urinalysis were performed before each cisplatin treatment. A CBC and platelet count were also performed 7 to 10 days after each cisplatin treatment.

Piroxicam[c] (0.3 mg/kg [0.14 mg/lb], PO, q 24 h) was administered starting 5 days before cisplatin administration. Initially, cisplatin[d] was administered at a dosage of 50 mg/m^2, IV, every 3 weeks with standard saline diuresis. The cisplatin dose was to be increased by 5 mg/m^2 in each group of 6 dogs until the MTD was reached. The MTD was defined as the highest dose of cisplatin administered that had no dogs with severe renal toxicosis or moderate renal toxicosis in ≤ 1 of 6 dogs (**Table 1**). Briefly, diuresis was induced in dogs by administering saline (0.9% NaCl) solution (18 mL/kg/h [8.2 mL/lb/h], IV) for 4 hours before and 2 hours after cisplatin administration.[15] Cisplatin was administered IV during a 20-minute period. Butorphanol[e] (0.4 mg/kg [0.18 mg/lb], IM) was administered 30 minutes before cisplatin to decrease vomiting.[16] Cisplatin treatment was delayed if the neutrophil count was < 3 × 10^3/mm^3 (reference range, 3 to 12 × 10^3/mm^3), the platelet count was < 50 × 10^3/mm^3 (reference range, 200 to 900 × 10^3/mm^3), the serum creatinine concentration was > 2.0 mg/dL (reference range, 0.5 to 1.5 mg/dL), or the BUN concentration was > 40 mg/dL (reference range, 7 to 32 mg/dL) without evidence of gastrointestinal hemorrhage. If there was evidence of gastrointestinal bleeding, the serum creatinine concentration was used to assess renal toxicosis. Treatment was reinstituted once the CBC and serum biochemical values were within reference limits. The renal values were rechecked weekly. If mild azotemia (BUN concentration < 40 mg/dL and serum creatinine concentration < 2.0 mg/dL) persisted, cisplatin was reinstituted, but the dosage was reduced by 20%.

Tumor responses were defined as follows: **complete remission (CR)**, complete resolution of measurable tumor; **partial remission (PR)**, ≥ 50% reduction in tumor volume with no new tumors; **stable disease (SD)**, < 50% change in tumor volume and no new tumors; and **progressive disease (PD)**, ≥ 50% increase in tumor volume or the development of new tumors. Tumor remission was objectively defined as CR or PR. Tumor measurements were performed on the tumor in 3 dimensions (rostrocaudal, mediolateral, and dorsoventral) and recorded in millimeters.

Information was recorded on all dogs and included tumor response, evidence of renal toxicosis determined by

Table 1—Criteria used to determine renal, hematologic, and gastrointestinal toxicosis after administration of cisplatin at various dosages in combination with piroxicam (0.3 mg/kg [0.14 mg/lb], PO, q 24 h) in 20 dogs with oral malignant melanoma (OMM) or oral squamous cell carcinoma (SCC)

Toxicosis	None	Mild	Moderate	Severe
Renal				
[a]BUN (mg/dL)	7–32	33–40	41–70	> 70
Serum creatinine (mg/dL)	0.5–1.5	1.6–1.9	2.0–3.5	> 3.5
Gastrointestinal				
Days of anorexia	0	≤ 1	2–3	> 3
Episodes of vomiting/day	0	1–2	> 2	Uncontrolled
Melena	No	No	Yes	Yes
Episodes of diarrhea/day	0	1–2	> 2	Uncontrolled
Supportive care needed	No	No	Yes	Yes
Hospitalization needed	No	No	No	Yes
Hematologic				
Neutrophil count (× 10^3/mm^3)	3–12	2–2.9	1–1.9	< 1
Platelet count (× 10^3/mm^3)	200–900	100–199	50–99	< 50

[a]If there was evidence of gastrointestinal hemorrhage, serum creatinine concentration alone was used to determine renal toxicosis.

serum biochemical analyses, clinical signs of gastrointestinal toxicosis, and evidence of hematologic toxicosis (myelosuppression) determined by CBC and platelet count (Table 1). If there was an increase in BUN concentration with evidence of tumor or gastrointestinal hemorrhage, renal toxicosis was defined by use of serum creatinine concentration alone.

Cisplatin pharmacokinetics—Blood samples were collected from dogs that received a combination of cisplatin (50 mg/m^2 [n = 6]; 55 mg/m^2 [5]) and piroxicam (0.3 mg/kg, q 24 h) in the clinical trial, with the exception of 1 dog that was not in the clinical trial, and from dogs not in the clinical trial that had nonurinary tract cancers and received cisplatin alone (55 mg/m^2 [n = 1]; 60 mg/m^2 [3]) after informed consent from the owners. Blood samples were collected in tubes that contained heparin at 0.25, 0.5, 0.75, 1.0, 2.0, and 4.0 hours after the first cisplatin administration. Samples were centrifuged within 1 hour of collection, and plasma was stored at –70°C until analyzed. Before analysis, an aliquot (100 µL) of plasma from each dog was thawed and centrifuged in special tubes[f] to collect the ultrafiltrate. The ultrafiltrate was then analyzed for free platinum by use of atomic absorption spectrometry.[g] The hollow cathode lamp current was 10 mA; the argon gas flow rate was 3 L/min, and flow was stopped during atomization. Twenty microliters of plasma ultrafiltrate was injected into the graphite tube of the spectrometer. The furnace temperature was held for 5 seconds at 85°C, then the temperature was increased for 50 seconds to 1,350°C (25 seconds each for drying and ashing). The temperature was then increased to 2,700°C (atomization) for 4 seconds, followed by a 3-second cleanout step at 2,850°C. The assay was linear from the range of 20 to 500 ng/mL. Control concentrations of platinum in 0.1N HCl were used. The coefficients of variation for the low control (50 ng/mL) and high control (400 ng/mL) were 2.5% and 0.88%, respectively. Samples found to contain < 20 ng of elemental platinum/mL were repeated, and a total of 60 µL was used. A total of 3 injections each consisting of 20 µL was introduced into the graphite tube; the instrument proceeded to the drying step after each injection. Following the last injection, the instrument proceeded through all steps and the platinum was quantitated.

A 2-compartment model was fitted to all measured cisplatin concentrations obtained from each dog by use of Bayesian estimation. Each observation was weighted by the inverse of the variance for the model prediction. Prior parameter distributions were determined on a subset of 5 dogs from this study and included the **volume of distribution (V_d)**, 10.0 L; elimination rate constant (ke), 0.6 hours^{-1}; internal rate constants for cisplatin (kcp), 1.663, and for piroxicam (kpc), 0.0136; and coefficients of variation for V_d, ke, kcp, and kpc, 50%, 33%, 100%, and 100%, respectively. The V_d, ke, kcp, and kpc were estimated parameters. Clearance and the elimination half-life of cisplatin were calculated by use of standard equations. Area under the curve was calculated by dividing the actual dose (mg) of cisplatin that was administered by the calculated clearance of cisplatin.

Statistical analyses—Data analyses were determined by use of standard statistical software,[h] and differences were considered to be significant at $P < 0.05$. Tumor response (remission vs stable or progressive disease) with the combined cisplatin and piroxicam treatment was compared with age, weight, sex, tumor type (OMM vs SCC), tumor location, gastrointestinal toxicosis, renal toxicosis, hematologic toxicosis, TNM stage, and cisplatin dose. Variables (age, weight, sex, tumor type, tumor location, hematologic toxicity, cisplatin dose, and initial serum creatinine concentration) were analyzed to determine if they were associated with presence of renal toxicosis after treatment with a combination of cisplatin and piroxicam. Categorical variables (sex, tumor type, tumor location, hematologic toxicosis, gastrointestinal toxicosis, and renal toxicosis) were compared by use of a Fisher exact test or χ^2 analysis.[17] Continuous variables (age, weight, cisplatin dose, and initial serum creatinine concentration) were compared by use of a Wilcoxon signed rank test.[18] Proportional hazards regression was used to determine if there was an association between age and survival and weight and survival.[18] Kaplan-Meier survival analyses were performed to determine if there was a significant difference in survival in relation to sex, tumor type (OMM vs SCC), tumor location, tumor response (remission vs stable or progressive disease), renal toxicosis, gastrointestinal toxicosis, hematologic toxicosis, TNM stage, and cisplatin dose.[19] Survival time was calculated from first treatment to death. Response duration was calculated from first treatment to progressive disease or death.

For pharmacokinetic studies, computer software[g] was used for pharmacokinetic modeling. Comparative and descriptive statistics were computed by use of statistical software.[i] Statistical determinations included least-squares regression analysis and the Wilcoxon rank sum test.

Results

Dogs and tumor characteristics—Twenty dogs were included in the cisplatin and piroxicam clinical trial (11 with OMM and 9 with SCC). Breeds of dogs included 6 mixed-breed dogs, 2 Cocker Spaniels, 2 Poodles, and 1 each of the following breeds: Dachshund, Labrador Retriever, Scottish Terrier, Miniature Schnauzer, Old English Sheepdog, Shetland Sheepdog, Yorkshire Terrier, Golden Retriever, Chow Chow, and Samoyed. There were 13 spayed female, 1 sexually intact male, and 6 castrated male dogs. Median weight of dogs was 12 kg (26.4 lb; range, 3.9 to 41.0 kg [8.6 to 90.2 lb]). Median age of dogs at study initiation was 11.6 years (range, 6 to 15 years). Information on tumor type and location included 6 maxillary (OMM [n = 4]; SCC [2]), 9 mandibular (OMM [5]; SCC [4]), 1 tongue (OMM), 3 tonsillar (SCC), and 1 oropharyngeal (OMM).

Maximum tolerated dose—In the dose escalation study, 6 dogs were initially treated with cisplatin (50 mg/m^2) combined with piroxicam with 6 hours of diuresis with saline (0.9% NaCl) solution. The cisplatin dose was then increased to 55 mg/m^2. Only 4 dogs were treated with this cisplatin dose because the toxicity exceeded the defined MTD. Renal toxicosis was determined to be mild in 2 dogs, moderate in 1 dog, and severe in 1 dog. Of the 4 dogs that received cisplatin at a dose of 55 mg/m^2 combined with piroxicam and 6 hours of diuresis with saline (0.9% NaCl) solution, 2 dogs also received IV fluid therapy overnight at the discretion of the clinician after treatment. The renal toxicity of cisplatin administered at a dose of 55 mg/m^2 exceeded what was defined for MTD. Therefore, it was determined that 50 mg/m^2 was the MTD of cisplatin when used in combination with piroxicam. Ten additional dogs were treated with cis-

platin (50 mg/m^2) in combination with piroxicam to further define the antitumor effect of cisplatin in combination with piroxicam.

Toxicity—Twenty dogs received the combination of cisplatin (16 dogs at 50 mg/m^2 and 4 dogs at 55 mg/m^2) and piroxicam. Seventeen dogs received ≥ 2 cisplatin treatments (10 dogs received 2 doses, 3 dogs received 3 doses, 2 dogs received 4 doses, and 1 dog received 5 and 6 doses). Of those 17 dogs, 4 dogs were administered the second cisplatin treatment at a reduced dose. From the 4 dogs that were treated with a reduced dose of cisplatin, 3 dogs received 40 mg/m^2 and 1 dog received 45 mg/m^2. There were 3 dogs that did not receive a second dose of cisplatin; the owner of 1 dog chose surgical treatment for the tumor, 1 dog had progressive disease but remained in the study, and 1 dog was euthanatized because of gastrointestinal toxicosis and the owner's decision to not continue with further treatment.

The combination of cisplatin and piroxicam was generally well tolerated. Of the 17 dogs that received the combination of cisplatin (50 mg/m^2) and piroxicam, renal toxicosis was observed in 7 dogs (mild [n = 4], moderate [2], and severe [1]). Although not all dogs developed azotemia, a mean increase of 0.4 mg/dL in serum creatinine concentration after 2 treatments with the combination of cisplatin (50 mg/m^2) and piroxicam was observed. Three dogs developed mild azotemia after 1 dose, and 3 dogs developed mild azotemia after 2 doses of cisplatin (50 mg/m^2) combined with piroxicam. After cisplatin was discontinued, the serum creatinine concentrations in all dogs returned to within reference limits. No dogs received additional cisplatin treatment if mild azotemia persisted. Evidence of hematologic toxicosis was infrequent. Thrombocytopenia was not detected in any dogs. Mild neutropenia (2.1 and 2.2 × 10^3/mm^3) was observed in 2 dogs. Similarly, clinical signs of gastrointestinal toxicosis were infrequent. Two dogs had clinical signs of mild gastrointestinal toxicosis, and 1 dog had clinical signs of severe gastrointestinal toxicosis, which resolved with supportive care. No significant association was found between renal toxicosis and body weight or initial serum creatinine concentration. Similarly, no association was found between gastrointestinal toxicosis and initial serum creatinine concentration, age, sex, and tumor type or location.

Response to treatment—Response to treatment was evaluated in 20 dogs **(Table 2)**. Tumor remission was observed in 2 of 11 dogs with OMM and 5 of 9 dogs with SCC; the overall rate of tumor remission was 35%. The tumor location in the 4 dogs with CR included 2 mandibular tumors (1 SCC [$T_3N_0M_0$] and 1 OMM [$T_{1a}N_{1a}M_0$]), 1 maxillary tumor (SCC [$T_3N_0M_0$]), and 1 oropharyngeal tumor (OMM [$T_2N_1M_0$]). Of dogs that had PR, 2 dogs had tonsilar tumors (SCC [$T_2N_1M_0$ and $T_2N_0M_0$]) and 1 dog had a mandibular tumor (SCC [$T_{2b}N_0M_0$]). Four dogs had SD (1 OMM, 3 SCC), and 9 dogs had PD (8 OMM, 1 SCC).

The median survival times were 119 days (range, 10 to 370 days) for dogs with OMM and 237 days (range, 41 to 2,010 days) for dogs with SCC. There was no significant difference between the tumor type and survival (P = 0.12). Dogs with CR or PR had a median survival time of 272 days (range, 85 to 1,687 days). Dogs with SD or PD had a median survival time of 116 days. Median response duration in 5 dogs was 142 days (range, 67 to 316 days). Two dogs had not reached progressive disease at 600 and 1,600 days (presently receiving piroxicam). There was a significant ($P < 0.02$) association between tumor response (remission) and longer survival. There was also a significant ($P < 0.025$) positive association between tumor response (remission) and tumor type (SCC). No association was observed between survival and age, sex, weight, tumor location, or initial serum creatinine concentrations.

Cisplatin pharmacokinetics—Cisplatin pharmacokinetic studies were completed in 15 dogs. This included 10 dogs with OMM or SCC in the clinical trial, 1 dog with OMM not in the clinical trial, 3 dogs with anal gland carcinoma, and 1 dog with nasal SCC. Eleven dogs received the combination treatment of cisplatin and piroxicam, and 4 dogs received cisplatin alone. Dogs included 8 spayed females, 1 sexually intact female, 5 castrated males, and 1 sexually intact male. Median age of dogs was 9.6 years (range, 6 to 15 years). Median body weight of dogs was 12.5 kg (27.5 lb; range, 4.8 to 44 kg [10.6 to 96.8 lb]). Dogs received cisplatin at doses of 50 mg/m^2 (n = 6), 55 mg/m^2 (6), and 60 mg/m^2 (3). There was no significant difference in sex or age between dogs receiving cisplatin alone (P = 0.2) or dogs receiving cisplatin in combination with piroxicam (P = 0.3). There was a significant (P = 0.02) difference between weight of dogs receiving cisplatin alone and dogs receiving cisplatin in combination with piroxicam.

The median **body surface area (BSA)** of the dogs was 0.54 m^2 (range, 0.28 to 1.25 m^2). Clearance of cisplatin varied 10-fold between dogs with a median of

Table 2—Response to 2 treatments of a combination of cisplatin (50 mg/m^2, IV, q 3 wk) and piroxicam (0.3 mg/kg, PO, q 24 h) in 20 dogs with OMM and SCC

Tumor response	OMM	SCC
Complete remission	2	2
Partial remission	0	3
Stable disease	1	3
Progressive disease	8	1

Table 3—Median and range of pharmacokinetic parameters of cisplatin (50, 55, and 60 mg/m^2, IV, q 3 wk) administered alone (n = 4) and in combination with piroxicam (0.3 mg/kg, PO, q 24 h [11]) in dogs with tumors

Parameter	Median	Range
ke (h^{-1})	0.52	0.05–0.56
V_d (L/m^2)	17.8	4.1–44.8
kcp (h^{-1})	1.43	0.54–6.01
kpc (h^{-1})	0.016	0.0026–0.041
Cl (mL/min/m^2)	152	35–418
AUC (mg/mL/min)	0.35	0.13–1.70

ke = Elimination rate constant. V_d = Volume of distribution. kcp = Internal rate constant for cisplatin. kpc = Internal rate constant for piroxicam. Cl = Clearance of cisplatin. AUC = Area under the curve.

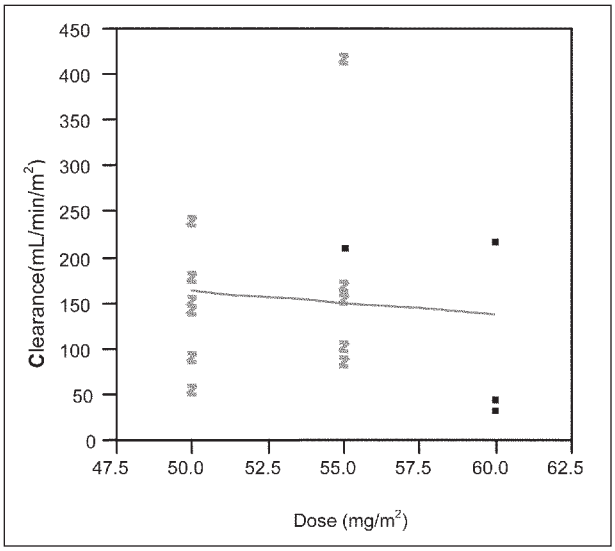

Figure 1—Association between clearance and dose of cisplatin (50, 55, and 60 mg/m^2, IV, q 3 wk) administered alone (closed squares [n = 4]) and in combination with piroxicam (0.3 mg/kg [0.14 mg/lb], PO, q 24 h; z [11]) in dogs with tumors. r^2 = 0.009.

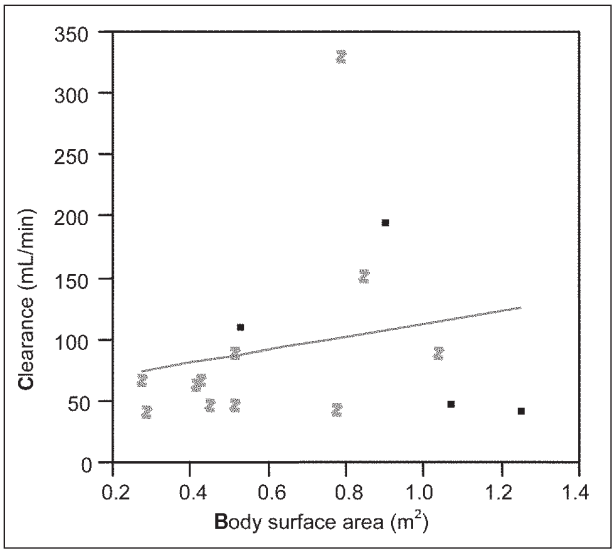

Figure 2—Association between body surface area and clearance of cisplatin (50, 55, and 60 mg/m^2, IV, q 3 wk) administered alone and in combination with piroxicam (0.3 mg/kg, PO, q 24 h) in dogs with tumors. r^2 = 0.042. *See* Figure 1 for key.

152 mL/min/m^2 (range, 35 to 418 mL/min/m^2; **Table 3**). Clearance of cisplatin did not change with increasing dose (P = 0.733; **Fig 1**) or with changes in BSA (P = 0.462; **Fig 2**). Cisplatin clearance in dogs that were treated with cisplatin alone was not significantly different from that in dogs that were treated with a combination of cisplatin and piroxicam (P = 0.648; **Fig 3**). The V_d for cisplatin in dogs that were treated with cisplatin alone was not significantly different from that in dogs that were treated with a combination of cisplatin and piroxicam (P = 0.648; **Fig 4**).

There was no significant difference in serum creatinine concentrations or in the change in WBC count or platelet count between dogs that were treated with a combination of cisplatin and piroxicam and those that were treated with cisplatin alone.

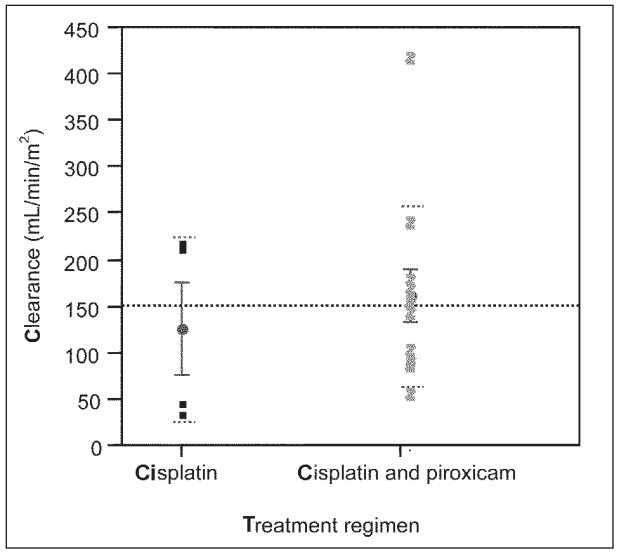

Figure 3—Clearance of cisplatin (50, 55, and 60 mg/m^2, IV, q 3 wk) administered alone and in combination with piroxicam (0.3 mg/kg, PO, q 24 h) in dogs with tumors. Dotted line represents overall mean. Error bars represent mean ± SE; short dotted lines represent SD. *See* Figure 1 for key.

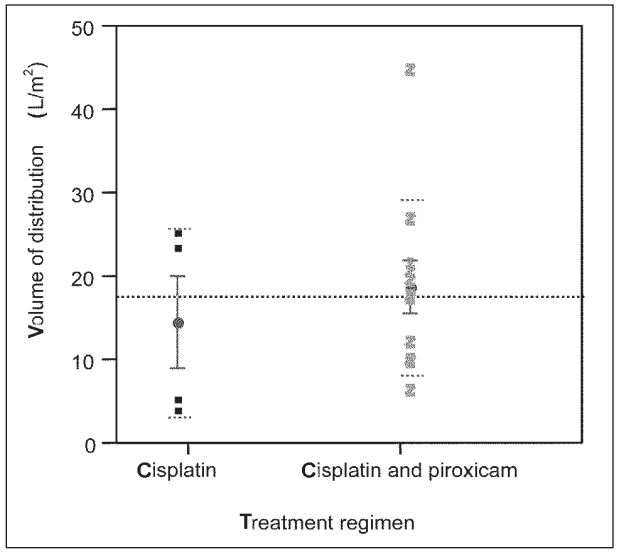

Figure 4—Volume of distribution of cisplatin (50, 55, and 60 mg/m^2, IV, q 3 wk) administered alone and in combination with piroxicam (0.3 mg/kg, PO, q 24 h) in dogs with tumors. *See* Figures 1 and 3 for key.

Discussion

A limited number of treatment studies[2,3,5-10,19] have been performed in dogs with oral cancer. To the authors' knowledge, this is the first prospective study that evaluated the effects of chemotherapy in nonresectable oral cancer. In our study, the MTD of cisplatin was 50 mg/m^2 when administered concurrently with piroxicam. Use of the MTD of cisplatin in combination with piroxicam had antitumor activity in OMM and SCC. Remission was observed more frequently in dogs with SCC (5/9 dogs) than dogs with OMM (2/11). Clearance of cisplatin was not different between dogs that were treated with a combination of cisplatin and piroxicam, compared with dogs that were treated with cisplatin alone.

The most common abnormality observed was

renal toxicosis, which developed in 7 of 20 dogs. This finding was expected given the combination of drugs. Cisplatin is directly toxic to renal tubular cells.[20] Piroxicam is a cyclooxygenase inhibitor that interferes with renal blood flow by inhibiting prostaglandins.[j] The maintenance of renal function is dependent on vasodilator prostaglandins.[j] Therefore, dogs with underlying renal dysfunction or renal insult are at an increased risk of renal ischemia when prostaglandin synthesis is reduced. During concurrent administration of cisplatin and piroxicam, it is important to closely monitor renal function and stop treatment or reduce the dosage of cisplatin if the serum creatinine concentration increases. Results of our study did not identify any factors that would predict the risk of renal toxicosis during treatment with a combination of cisplatin and piroxicam. The evaluation of renal function by use of serum creatinine and BUN concentrations has limitations. Both tests are insensitive and do not detect renal dysfunction until glomerular filtration rate is reduced to ≤ 25%. Therefore, it may be possible that small changes in renal function were not detected by use of these tests in our study. Other tests such as quantitative renal scintigraphy or endogenous creatinine clearance test may be more sensitive for evaluation of subclinical renal insufficiency.

The pharmacokinetics of cisplatin were studied to determine the effects of concurrent piroxicam treatment on cisplatin pharmacokinetics. Both piroxicam and cisplatin are extensively bound to plasma proteins. In theory, piroxicam could alter cisplatin pharmacokinetics by interfering with protein binding of cisplatin, and this could contribute to the antitumor effects and toxicity. However, results of our study indicated that there was no difference in the clearance or V_d of free cisplatin between dogs treated with a combination of cisplatin and piroxicam and dogs treated with cisplatin alone. Pharmacokinetic parameters were not affected by BSA or different doses of cisplatin. Therefore, the enhanced antitumor effects observed when piroxicam was added to cisplatin were not believed to be caused by altered pharmacokinetics of cisplatin. This information is important for elucidation of the mechanisms involved in the antitumor activity of a combination of cisplatin and piroxicam.

In our study, the pharmacokinetic results for cisplatin obtained in 15 dogs indicated substantial interpatient variability with a 10-fold difference in cisplatin clearance. This variability has been observed with use of other chemotherapeutic agents.[21]

The response rate in this study was documented in 2 of 11 dogs with OMM and 5 of 9 with SCC. This response rate in SCC appears higher than remission rates in other studies[2,5,6] that evaluated other chemotherapy agents or piroxicam alone in oral tumors. This antitumor activity could be caused by the additive effects of piroxicam when administered in combination with cisplatin. Results of 1 study[13] suggest that the addition of piroxicam to cisplatin treatment results in at least an additive response to treatment in urinary bladder cancer in dogs. Cyclooxygenase-2 is expressed in SCC[22] in dogs and in certain dogs with OMM.[23] In addition, high concentrations of prostaglandin E_2 have been found in SCC.[24] Cyclooxygenase products, including prostaglandin E_2, have been incriminated for a role in tumor formation and progression, tumor angiogenesis, and resistance to apoptosis in the tumor. Treatment of urinary bladder cancer in dogs with piroxicam has resulted in the induction of apoptosis.[12] This finding may be important because the killing of cells with cisplatin is dependent on the tumor cells undergoing apoptosis.[25]

Results of our study indicate that treatment with a combination of cisplatin and piroxicam had antitumor activity against SCC in dogs. Cisplatin (50 mg/m^2, IV, q 3 wk) administered in combination with piroxicam (0.3 mg/kg, PO, q 24 h) offers a treatment option with acceptable toxicity when renal function is carefully monitored for dogs with OMM and SCC. In addition, by studying and understanding the mechanisms of the antitumor activity, this treatment may have application to other forms of solid cancers. Future studies should include those with cyclooxygenase-2 specific inhibitors to determine if similar antitumor effects can be obtained with less toxicity.

[a]Guptill L, Knapp DW, Hahn K, et al. Retrospective study of *cis-diamminedichloroplatinum* II (cisplatin) treatment for canine malignant melanoma (abstr), in *Proceedings*. Vet Cancer Soc 1993;65.
[b]Knapp DW. Purdue Comparative Oncology Program, Department of Veterinary Clinical Science, Purdue University, West Lafayette, Ind: Unpublished data, 2000.
[c]Piroxicam, Pfizer, New York, NY.
[d]Cisplatin, Bristol Laboratories, Bristol-Myers Squibb Co, Princeton, NJ.
[e]Butorphanol, Fort Dodge Laboratories, Fort Dodge, Iowa.
[f]Amicon ultrafiltrate tubes, Centricon, Millipore Corp, Bedford, Mass.
[g]Varian spectra atomic absorption 400, Varian Inc, Victoria, Australia.
[h]SAS System, version 8.2, SAS Institute Inc, Cary, NC.
[i]Adapt II software, Biomedical simulation resource, University of Southern California, Los Angeles, Calif.
[j]Vane J, Botting R. Anti-inflammatory drugs and their mechanism of action (abstr). *Inflammation Res* 1998;47.

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New Veterinary Biologic Products

Product name	Species and indications for use	Route of administration	Remarks
Encephalomyelitis-West Nile Virus Vaccine, Eastern, Western, and Venezuelan, Killed Virus, Tetanus Toxoid (Wyeth, US Vet Lic No. 112)	For vaccination of healthy horses as an aid in the prevention of viremia caused by West Nile Virus, and as an aid in the prevention of equine encephalomyelitis caused by Eastern, Western, and Venezuelan viruses, and tetanus	IM	USDA licensed 10/27/03
Bovine Rotavirus-Coronavirus Vaccine, Killed Virus, *Clostridium perfringens* Type C & D-*Escherichia coli* Bacterin-Toxoid (Schering-Plough Animal Health Corp, US Vet Lic No. 165A)	For use in healthy heifers and cows as an aid in the prevention of neonatal calf diarrhea caused by enterotoxigenic *E coli* pilus type K99 and bovine Group A rotaviruses and enterotoxemia caused by *C perfringens* Types C & D and as an aid in the control of neonatal calf diarrhea caused by bovine coronaviruses	SC	USDA licensed 11/17/03