Evaluation of cisplatin administered with piroxicam in dogs with transitional cell carcinoma of the urinary bladder

Shawna N. Greene, DVM; Michael D. Lucroy, DVM, MS, DACVIM; Chelsea B. Greenberg, DVM, MS; Patty L. Bonney, BS; Deborah W. Knapp, DVM, MS, DACVIM

Objective—To evaluate the antitumor activity and toxic effects of a conservative dose of cisplatin administered in combination with piroxicam to dogs with transitional cell carcinoma (TCC) of the urinary bladder.

Design—Clinical trial (nonrandomized, noncontrolled).

Animals—14 client-owned dogs with histologically confirmed TCC of the urinary bladder.

Procedures—Each dog was treated with cisplatin (50 mg/m², IV, q 21 d [reduced to 40 mg/m², IV, q 21 d because of toxic effects]) and piroxicam (0.3 mg/kg [0.14 mg/lb], PO, q 24 h). A CBC, serum biochemical analyses, and urinalysis were performed prior to each cisplatin treatment. Tumor staging (determined from thoracic and abdominal radiographic and urinary bladder ultrasonographic findings) was performed before treatment and at 6-week intervals during treatment.

Results—5 dogs received only 1 dose of cisplatin because of the rapid progression of disease (n = 2) or toxic effects (3). With regard to the neoplastic disease among the other 9 dogs, 1 had partial remission, 5 had stable disease, and 3 had progressive disease after 6 weeks of treatment. Median progression-free interval was 78 days (range, 20 to 112 days). Median survival time was 307 days (range, 29 to 929 days). Moderate to severe renal toxicosis and moderate to severe gastrointestinal toxicosis developed in 5 and 8 dogs, respectively.

Conclusions and Clinical Relevance—Because of minimal efficacy and associated renal and gastrointestinal toxicosis, administration of cisplatin (40 to 50 mg/m²) with piroxicam cannot be recommended for treatment of dogs with TCC of the urinary bladder. (*J Am Vet Med Assoc* 2007;231:1056–1060)

Transitional cell carcinoma is the most common tumor in the urinary bladder of dogs, representing approximately 2% of all reported canine cancers.[1,2] Numerous treatments for urinary bladder TCC in dogs have been evaluated including surgery, radiation therapy, photodynamic therapy, and chemotherapy.[3-5] Surgical intervention has been largely unrewarding because of the typical trigonal tumor location (where complete resection is not possible) and the potential for metastatic and recurrent disease.[2,4] Full-course and intraoperative radiation therapy can be effective against TCC, but urinary bladder fibrosis, urinary incontinence, cystitis, and toxic effects in surrounding organs have been common posttreatment complications.[5-8] Photodynamic therapy has shown some promise but is not widely available. Various single-agent chemotherapeutic protocols have been evaluated, including administrations of carboplatin, cisplatin, doxorubicin, and mitoxantrone. These drugs have limited efficacy against urinary bladder TCC in dogs and are associated with remission rates of 0% to 25% and survival times of 130 to 180 days.[9-14]

Abbreviation

TCC	Transitional cell carcinoma

Piroxicam, a nonsteroidal anti-inflammatory drug, has also been evaluated for the treatment of dogs with TCC of the urinary bladder.[2,15-17] Although the exact mechanisms of the antitumor activity of piroxicam have not been completely defined, piroxicam induces apoptosis in TCCs and appears to have antiangiogenic effects.[17] Piroxicam, administered as a single agent or in combination with chemotherapeutic agents, has been effective against urinary bladder TCC in dogs (**Appendix 1**).[2,15-18] On the basis of a published report,[15] the combination of cisplatin (60 mg/m²) and piroxicam for the treatment of TCC in dogs appears to have the most promising antitumor effects but has also caused dose-limiting renal toxicosis. Renal toxicosis developed in 12 of 14 dogs given cisplatin and piroxicam and in 4 of 8 dogs given cisplatin alone in a randomized clinical trial.[15] The nephrotoxicity of cisplatin-piroxicam combinations is believed to be a result of direct cisplatin-associated damage to the proximal and distal renal tubule cells and a reduction in renal blood flow caused by both cisplatin and piroxicam.[15,19] The renal toxicity

From the Purdue Comparative Oncology Program, Department of Veterinary Clinical Sciences, School of Veterinary Medicine (Greene, Lucroy, Greenberg, Bonney, Knapp), and Purdue Cancer Center (Lucroy, Knapp), Purdue University, West Lafayette, IN 47907.

Presented, in part, at the 24th Annual Veterinary Cancer Society Conference, Kansas City, Mo, November 2004.

Address correspondence to Dr. Knapp.

of cisplatin is dose-related.[20] Therefore, lowering the dose of cisplatin that has been typically used in cisplatin-piroxicam combinations could result in less frequent development of renal toxicosis among treated dogs. The purpose of the study reported here was to evaluate the antitumor activity and toxic effects of a low dose of cisplatin administered in combination with piroxicam to dogs with TCC of the urinary bladder.

Materials and Methods

Animals—The study was approved by the Purdue University Animal Care and Use Committee. The study was designed to follow a modified Gehan's 2-stage phase-II clinical trial design.[21] Following this design, 14 client-owned dogs were to be initially entered into the study. If at least 1 dog had remission and drug-associated toxic effects were considered acceptable, then additional dogs were to be entered to better estimate the remission rate. If no remissions occurred or severe adverse effects of treatment developed at an unacceptable frequency among the first 14 dogs, the trial would be concluded. For inclusion in the study, dogs had to have naturally occurring, histologically confirmed, measurable TCC of the urinary bladder and had to have received no prior treatment; written owner consent was also required.

For each dog, evaluations performed before and at 6-week intervals during treatment included a CBC, serum biochemical analyses, urinalysis, microbial culture and susceptibility testing of urine, thoracic radiography (right and left lateral and ventrodorsal radiographic views), abdominal radiography (right lateral and ventrodorsal radiographic views), and abdominal ultrasonography. The urinary bladder masses were measured in a manner similar to that described by Chun et al.[9] Tumor staging followed the World Health Organization criteria that have been established for urinary bladder tumors in dogs (**Appendix 2**).[22]

Treatment—Cisplatin[a] (50 mg/m², IV [a more commonly used dose is 60 mg/m²]) was administered during a 20-minute period every 3 weeks. A 6-hour period of standard saline (0.9% NaCl) solution diuresis (18 mL of saline solution/kg/h [8.2 mL/lb/h]) was provided during the 4 hours before and 2 hours after cisplatin treatment.[16] Dogs were given butorphanol[b] (0.4 mg/kg [0.18 mg/lb], IV) 30 minutes prior to cisplatin administration and at the end of the diuresis. Beginning on the first day of the cisplatin administration, all dogs were given piroxicam (0.3 mg/kg [0.14 mg/lb]) orally once daily throughout the study.

Assessments—For each dog, a CBC, serum biochemical analyses, and urinalysis were performed prior to each cisplatin treatment; a CBC and platelet count were performed 10 to 14 days after each cisplatin treatment. Cisplatin treatment was delayed if the neutrophil count was < 3,000 cells/µL (reference range, 3,000 to 12,000 neutrophils/µL), if the platelet count was < 50,000 platelets/µL (reference range, 200,000 to 500,000 platelets/µL), or if the serum creatinine concentration was > 1.5 mg/dL (reference range, 0.5 to 1.5 mg/dL). If treatment was delayed, the aforementioned variables were reevaluated weekly until the neutrophil and platelet counts were within reference ranges and the serum creatinine concentration was < 1.5 mg/dL. The dose of cisplatin was then administered at a reduced dosage (approx 20% reduction from the previous dose). If the serum creatinine concentration did not return to within reference range, cisplatin administration was discontinued.

The antitumor effects of treatment were assessed in each dog at 6-week intervals (3 weeks following the second, fourth, sixth, and so forth cisplatin doses). Complete remission was defined as complete resolution of all measurable portions of the TCC. Partial remission was defined as ≥ 50% decrease in tumor volume and no development of new tumor lesions. Stable disease was defined as < 50% change in tumor volume and no development of new tumor lesions. Progressive disease was defined as ≥ 50% increase in tumor volume or development of new tumor lesions. Dogs with evidence of remission or stable disease continued to receive the same treatment. The treatment protocol was scheduled to be followed until 2 doses of cisplatin were given after complete remission was detected, until progressive disease was detected, or until unacceptable toxic effects (assessed by the attending veterinarian or pet owner) developed. In instances of treatment failure (ie, for dogs with progressive disease or unacceptable toxic effects), alternative treatments were offered. The progression-free interval in dogs with complete or partial remission was defined as the interval from the first cisplatin treatment until progressive disease was detected. Survival time was defined as the interval from the first cisplatin treatment until death. Evidence of toxicosis was recorded and categorized as renal, gastrointestinal, or hematologic (**Appendix 3**).

Statistical analysis—Data are reported as mean ± SD or median and range. Median survival times were calculated by use of the Kaplan-Meier product-limit method, and the survival times were compared by use of the log-rank test. Categorical variables were compared by use of a Fisher exact test. All analyses were performed with statistical software.[c] Values of $P < 0.05$ were considered significant.

Results

Fourteen dogs were entered into the study. Dogs were treated between 2001 and 2003 at the Purdue University Veterinary Teaching Hospital. There were 8 spayed females and 6 neutered males. Breeds included mixed (n = 4), Scottish Terrier (3), Shetland Sheepdog (2), Beagle (2), German Wirehaired Pointer (1), West Highland White Terrier (1), and Miniature Poodle (1). Mean ± SD weight of the dogs was 13.1 ± 7.1 kg (28.8 ± 15.6 lb), and mean age at the time of diagnosis was 10.3 ± 3.6 years. With regard to tumor staging, 5 dogs were classified as T2N0M0, 8 dogs were classified as T3N0M0, and 1 dog was classified as T3N1M0. Dogs received 1 to 5 doses of cisplatin (median, 3 doses). Nine dogs were initially administered 40 mg/m² doses of cisplatin, and 5 dogs were administered 50 mg/m² doses of cisplatin. All dogs received 0.3 mg of piroxicam/kg orally continuously throughout the study. The

frequency and severity of toxic effects in dogs given 50 mg of cisplatin/m^2 prompted the change to a lower initial dose of cisplatin (40 mg/m^2).

Nine of the 14 dogs received at least 2 doses of cisplatin. Tumor response in these 9 dogs after 2 doses of cisplatin included partial remission in 1 dog, stable disease in 5 dogs, and progressive disease in 3 dogs. Five dogs received only 1 dose of cisplatin because of rapidly progressing disease in 2 dogs and unacceptable toxic effects in 3 dogs.

In 12 dogs for which disease progression data were available, the median progression-free interval was 78 days (range, 20 to 112 days). The median progression-free interval for dogs treated with 40 mg/m^2 doses of cisplatin was not significantly (P = 0.514) different from the interval for dogs treated with 50 mg/m^2 doses of cisplatin (78 and 71 days, respectively). After treatment failure following administration of the low dose of cisplatin combined with piroxicam, 10 dogs received various treatments including administrations of mitoxantrone, doxorubicin, gemcitabine, and deracoxib. The overall median survival time was 307 days (range, 29 to 929 days). The median overall survival time of dogs that were initially treated with 40 mg of cisplatin/m^2 and piroxicam was not significantly (P = 0.224) different from that of dogs treated with 50 mg of cisplatin/m^2 and piroxicam (321 and 145 days, respectively).

Toxic effects were common among dogs treated with 40 or 50 mg of cisplatin/m^2 and piroxicam (**Table 1**). After 1 or 2 doses of cisplatin, 4 of the 14 (29%) dogs developed moderate or severe renal toxicosis. On the basis of data obtained after all cisplatin doses, renal toxicosis was evident in 12 dogs and was categorized as mild in 7 dogs, moderate in 4 dogs, and severe in 1 dog. In these 12 dogs, the mean maximum creatinine concentration within 3 weeks of cisplatin administration was 2.83 ± 3.54 mg/dL. Gastrointestinal toxicosis was also common. Treatment-related toxic effects contributed to the decision to discontinue cisplatin administration in 10 of the 14 dogs. There were no significant differences in the proportion of dogs with either renal or gastrointestinal toxic effects between those treated with 40 mg of cisplatin/m^2 and those treated with 50 mg of cisplatin/m^2 (P = 0.506 and 0.491, respectively).

All dogs were eventually euthanatized because of progressive disease. Postmortem examination was performed in 3 dogs. Of those 3 dogs, all had TCC within the urinary bladder and urethra, hydronephrosis, and pyelonephritis. Two of the dogs had TCC in regional lymph nodes (sacral and lumbar lymph nodes) and distant TCC metastases to the abdominal wall, lumbosacral vertebral bodies, and lungs.

Discussion

The purpose of the present study was to determine whether doses of 40 or 50 mg of cisplatin/m^2 administered at 21-day intervals in combination with once-daily treatment with piroxicam would induce remission of TCC of the urinary bladder without causing unacceptable toxic effects in dogs. Although promising antitumor effects have been associated with a protocol involving a combination of 60 mg of cisplatin/m^2 with 0.3 mg of piroxicam/kg,[15] the reduced dosage of cisplatin used in the present study (combined with piroxicam) had minimal antitumor effects and resulted in toxicoses in 12 of 14 treated dogs. Because of renal toxicosis and lack of tumor response to this conservative-dose cisplatin regimen, it is currently not recommended for the treatment of urinary bladder TCC in dogs. Furthermore, because of the renal toxic effects associated with the cisplatin (60 mg/m^2)-piroxicam (0.3 mg/kg) combination protocol, that particular higher-dose cisplatin regimen is also not recommended. The decreased dosage of cisplatin was a likely reason for lack of efficacy in the present study, given that the tumor characteristics (TMN stage and grade of tumor) and age, sex, and breed

Table 1—Assessments of renal and gastrointestinal toxic effects in 14 dogs with TCC of the urinary bladder following treatment* with 1, 2, or ≥ 3 doses of cisplatin (40 or 50 mg/m^2, IV, q 21 d) and piroxicam (0.3 mg/kg [0.14 mg/lb], PO, q 24 h).

System affected	No. of cisplatin doses after which effect was detected	Classification of effect				Total No. of dogs receiving that No. of doses
		None	Mild	Moderate	Severe	
Renal	40 mg/m^2					
	1	8	1	0	0	9
	2	5	0	1	1	7
	≥ 3	1	4	1	0	6
	50 mg/m^2					
	1	2	1	2	0	5
	2	2	0	0	0	2
	≥ 3	0	1	1	0	2
Gastrointestinal						
	40 mg/m^2					
	1	4	1	4	0	9
	2	3	2	1	1	7
	≥ 3	2	2	0	2	6
	50 mg/m^2					
	1	0	1	2	2	5
	2	0	1	1	0	2
	≥ 3	0	1	0	1	2

*Nine dogs were initially administered 40 mg/m^2 doses of cisplatin, and 5 dogs were administered 50 mg/m^2 doses of cisplatin. Because of the frequency and severity of toxic effects in dogs given 50 mg of cisplatin/m^2, the initial dose of cisplatin was reduced. Overall, treatment-related toxic effects contributed to the decision to discontinue cisplatin administration in 10 of the 14 dogs.

of the affected dogs were similar to those of study populations in other investigations involving dogs with urinary bladder TCC.[15,16,18]

Development of renal toxicosis in association with combinations of cisplatin and piroxicam for treatment of urinary bladder TCC in dogs has been reported previously.[15] However, dogs with non–urinary tract tumors that were treated with cisplatin and piroxicam in another study[23] developed less frequent and less severe toxicoses. This finding may be attributable to the presence and progression of the TCC within the lower portion of the urinary tract, which resulted in decreased renal function secondary to partial or complete outflow obstruction, persistent urinary tract infections, or possible spread of TCC into the kidneys.

The present study was based on Gehan's 2-stage phase-II study design, which dictated that detection of a positive response in 1 of 14 dogs was sufficient evidence of antitumor activity for enrollment of additional dogs (if drug-associated toxic effects were considered acceptable). Although all 14 dogs should have been treated with a protocol involving 50 mg of cisplatin/m^2 to follow the clinical trial design, the frequency and severity of the toxic effects associated with that treatment were not considered appropriate for continuing the administration of that dose to dogs at the time of enrollment into the study. Consequently, the dose of cisplatin administered initially was decreased to 40 mg/m^2. Among the 14 dogs, partial remission was evident in only 1 (7%). Other protocols that are associated with less frequent and less severe toxic effects have resulted in higher remission rates (20% to 40%) of TCC in dogs.[2,18]

One interesting finding of the present study was the relatively long median survival time (overall, 307 days; 321 days for dogs receiving 40 mg of cisplatin/m^2), compared with results from other studies (Appendix 1). The reasons for the favorable outcome are not known. Most dogs in the study continued to be treated with a cyclooxygenase inhibitor until death, and 4 dogs received other treatments too. Also, because of the small sample size included in the present study, it is not possible to know whether survival times among a larger number of dogs treated in a similar fashion would be similar. Furthermore, the small sample size prevents definitive comparison of the results of the present study with those of other investigations. Because of the toxic effects detected in the dogs of the present study, other treatment protocols that are associated with less frequent and less severe toxicoses should be considered for the treatment of dogs with TCC of the urinary bladder, including mitoxantrone combined with piroxicam (survival time, 291 days[18]) or piroxicam alone (survival time, 195 days[2,16]).

On the basis of the results of the study reported here, a treatment protocol involving 40 to 50 mg/m^2 doses of cisplatin combined with piroxicam is not recommended for dogs with TCC of the urinary bladder because of the toxic effects that frequently developed among treated dogs and the limited number of dogs in which remission was achieved. Alternative treatment strategies that take advantage of the synergistic effects (and likely decreased toxicity) of cyclooxygenase inhibitors in combination with chemotherapy should be investigated.

a. Bristol-Myers Squibb Co, New York, NY.
b. Torbugesic, Fort Dodge Labs, Fort Dodge, Iowa.
c. SAS, version 9.0, SAS Institute Inc, Cary, NC.

References

1. Norris AM, Laing EJ, Vallie VE, et al. Canine bladder and urethral tumors: a retrospective study of 115 cases (1980–1985). *J Vet Intern Med* 1992;6:145–153.
2. Mutsaers AJ, Widmer WR, Knapp DW. Canine transitional cell carcinoma. *J Vet Intern Med* 2003;17:136–144.
3. Lucroy MD, Ridgway TD, Peavy GM, et al. Preclinical evaluation of 5-aminolevulinic acid-based photodynamic therapy for canine transitional cell carcinoma. *Vet Comp Oncol* 2003;2:76–85.
4. Stone EA, George TF, Gilson SD, et al. Partial cystectomy for bladder neoplasia: surgical technique and outcome in 11 dogs. *J Small Anim Pract* 1996;37:480–485.
5. Anderson CR, McNiel EA, Gillette EL, et al. Late complication of pelvic radiation in 16 dogs. *Vet Radiol Ultrasound* 2002;43:187–192.
6. Poirier VJ, Forrest LJ, Adams WM, et al. Piroxicam, mitoxantrone, and course fraction radiotherapy for the treatment of transitional cell carcinoma of the bladder in 10 dogs: a pilot study. *J Am Anim Hosp Assoc* 2004;40:131–136.
7. Walker M, Breider M. Intraoperative radiotherapy of canine bladder cancer. *Vet Radiol* 1987;28:200–204.
8. Withrow SJ, Gillette EL, Hoopes PJ, et al. Intraoperative irradiation of 16 spontaneously occurring canine neoplasms. *Vet Surg* 1989;18:7–11.
9. Chun R, Knapp DW, Widmer WR. Phase II clinical trial of carboplatin in canine transitional cell carcinoma of the urinary bladder. *J Vet Intern Med* 1997;11:279–283.
10. Chun R, Knapp DW, Widmer WR, et al. Cisplatin treatment of transitional cell carcinoma of the urinary bladder in dogs: 18 cases (1983–1993). *J Am Vet Med Assoc* 1996;209:1588–1591.
11. Helfand SC, Hamilton TA, Hungerford LL, et al. Comparison of three treatments for transitional cell carcinoma of the bladder in the dog. *J Am Anim Hosp Assoc* 1994;30:270–275.
12. Moore AS, Cardona A, Shapiro W, et al. Cisplatin (cisdiammineidichloroplatinum) for treatment of transitional cell carcinoma of the urinary bladder or urethra. A retrospective study of 15 dogs. *J Vet Intern Med* 1990;4:148–152.
13. Ogilvie GK, Obradovich JE, Elmslie RE, et al. Efficacy of mitoxantrone against various neoplasms in dogs. *J Am Vet Med Assoc* 1991;198:1618–1621.
14. Shapiro W, Kitchell BE, Fossum TW, et al. Cisplatin for treatment of transitional cell and squamous cell carcinomas in dogs. *J Am Vet Med Assoc* 1988;193:1530–1533.
15. Knapp DW, Glickman NW, Widmer WR, et al. Cisplatin versus cisplatin combined with piroxicam in a canine model of human invasive urinary bladder cancer. *Cancer Chemother Pharmacol* 2000;46:221–226.
16. Knapp DW, Richardson RC, Chan TC, et al. Piroxicam therapy in 34 dogs with transitional cell carcinoma of the urinary bladder. *J Vet Intern Med* 1994;8:273–278.
17. Mohammed SI, Bennett PF, Craig BA, et al. Effects of the cyclooxygenase inhibitor, piroxicam, on tumor response, apoptosis, and angiogenesis in a canine model of human invasive urinary bladder cancer. *Cancer Res* 2002;62:356–358.
18. Henry CJ, McCaw DL, Turnquist SE. Clinical evaluation of mitoxantrone and piroxicam in a canine model of human invasive urinary bladder carcinoma. *Clin Cancer Res* 2003;9:906–911.
19. Schlondorff D. Renal complications of nonsteroidal anti-inflammatory drugs. *Kidney Int* 1993;44:643–653.
20. Schwerdt G, Freudinger R, Schuster C, et al. Cisplatin-induced apoptosis is enhanced by hypoxia and by inhibition of mitochondria in renal collecting duct cells. *Toxicol Sci* 2005;85:735–742.
21. Introduction to clinical trials. In: Friedman LM, Furberg CD, DeMets DL, eds. *Fundamentals of clinical trials*. 3rd ed. St Louis: Mosby, 1996;1–15.
22. Owens L. *TNM classification of tumors in domestic animals*. Geneva: World Health Organization, 1980;34.
23. Boria PA, Murry DJ, Bennett PF, et al. Evaluation of cisplatin combined with piroxicam for the treatment of oral malignant melanoma and oral squamous cell carcinoma in dogs. *J Am Vet Med Assoc* 2004;224:388–394.

Appendix 1

Results of selected chemotherapy protocols for the treatment of dogs with TCC of the urinary bladder.

Treatment	No. of dogs treated	Remission* (%)	Median survival time (d)	Reference
Piroxicam	62	18	195	2, 16, 17
Piroxicam and mitoxantrone	48	35.4	291	18
Piroxicam and cisplatin (60 mg/m^2)	14	71.4	246	15
Cisplatin (60 mg/m^2)	25	12	130	2, 10

*Complete or partial remission.

Appendix 2

World Health Organization clinical (TMN) staging of urinary bladder tumors in dogs.[22]

Category	Description
T	
Tis	Carcinoma in situ
T0	No evidence of tumor
T1	Superficial papillary tumor
T2	Tumor invading the bladder wall with induration
T3	Tumor invading neighboring organs
N	
N0	No evidence of regional lymph node involvement
N1	Regional lymph node involved
N2	Regional lymph node and neighboring lymph node involved
M	
M0	No evidence of distant metastasis
M1	Distant metastasis detected

Appendix 3

Classification of renal, gastrointestinal, and hematologic toxic effects associated with combined cisplatin-piroxicam treatment of dogs with TCC of the urinary bladder.

	Classification			
Variable	None	Mild	Moderate	Severe
Renal				
Serum creatinine (mg/dL)	0.5–1.5	1.6–2.0	2.1–3.5	> 3.5
Gastrointestinal				
Duration of anorexia (d)	0	≤ 1	2–3	> 3
No. of vomiting episodes	0	1–2	> 2	Uncontrolled
Melena	No	No	Yes	Yes
No. of diarrhea episodes	0	1–2	> 2	Uncontrolled
Supportive care required	No	No	Yes	Yes
Hospitalization required	No	No	No	Yes
Hematologic				
Neutrophils (× 10^3 cells/μL)	3.0–12.0	2.0–2.9	1.0–1.9	< 1.0
Platelets (× 10^3 platelets/μL)	200–900	100–199	50–99	< 50