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ORIGINAL ARTICLE

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Cisplatin versus cisplatin combined with piroxicam in a canine model of human invasive urinary bladder cancer

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Abstract *Purpose*: More than 12,000 people are expected to die from invasive transitional cell carcinoma (TCC) of the urinary bladder each year in the United States, indicating that more effective therapy is needed. Drugs inhibiting cyclooxygenase (cox) have recently been found to have chemopreventive and antitumor activity and may potentiate the effects of chemotherapy. The purpose of this study was to determine whether cisplatin combined with the cox-inhibitor piroxicam would induce remission more frequently than cisplatin alone in a relevant animal model of human invasive TCC. *Methods*: Pet dogs with naturally occurring, histopathologically confirmed, measurable TCC of the urinary bladder were randomized to receive cisplatin (60 mg/m^2 i.v. every 21 days) or cisplatin (same dosage) combined with piroxicam (0.3 mg/kg orally every 24 h). Complete staging was performed prior to and at 6-week intervals during therapy. *Results*: After eight dogs had been evaluated in each treatment group, a significant difference in remission rate was noted (Fisher's Exact test, $P < 0.004$). Tumor responses in the cisplatin/piroxicam group included two complete remissions (CR), four partial remissions (PR), two stable disease (SD), and no progressive disease (PD). Tumor responses to cisplatin alone in eight dogs were no CR, no PR, four SD, and four PD. Six additional dogs were treated with cisplatin/piroxicam, and in total 10 of 14 dogs had remission (two CR, eight PR). Renal toxicity of cisplatin/piroxicam was frequent and dose limiting. *Conclusions*: Cisplatin/piroxicam induced remission more frequently than cisplatin alone in a canine model of human invasive TCC. Strategies to reduce renal toxicity need to be developed prior to evaluation of cisplatin/piroxicam in humans or general use of this treatment in pet dogs.

Key words Bladder cancer · Animal models · Piroxicam · Cisplatin · Cox inhibitors

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Introduction

Transitional cell carcinoma (TCC) of the urinary bladder is diagnosed in more than 54,000 people and results in more than 12,000 deaths each year in the United States alone [24]. Most bladder cancer deaths are due to invasive TCC which has metastasized and is resistant to chemotherapy [24]. Strategies to improve the efficacy of chemotherapy may lead to a decrease in mortality related to TCC.

Recently, cyclooxygenase (cox) inhibitors have been shown to have chemopreventive and antitumor activity in chemically induced rodent bladder tumors, in pet dogs with naturally occurring invasive TCC, and in colon cancer and other malignancies in humans [3, 14, 18, 19, 22, 26]. The effects of cox inhibitors in spontaneous canine TCC are especially interesting because canine TCC bears a very close resemblance to human invasive TCC and serves as a model of that cancer. Invasive TCC in dogs and humans is similar in: histopathological characteristics (>80% invasive, intermediate to high grade); biological behavior (clinical stage at diagnosis, metastasis, survival); and response to single-agent chemotherapy [13, 16]. In addition to the antitumor activity of cox inhibitors as single agents, there is interest in the effects of combined chemotherapy and cox inhibitor therapy.

Cisplatin has antitumor activity against human bladder cancer [24]. Remission has been noted in 17% to 40% of patients receiving cisplatin as a single agent and in 50% to 70% of patients treated with cisplatin combined with other chemotherapeutic agents [24]. The purpose of this study was to determine whether piroxicam combined with cisplatin would induce remission more frequently than cisplatin alone in canine TCC. In this canine bladder cancer model, cisplatin has similar activity (12–20% remission rate as a single agent) to the activity of cisplatin in human TCC [5, 12, 16], Given as a single agent, the cox inhibitor piroxicam has induced remission in 17% of dogs with TCC [14].

Table 1 World Health Organization clinical staging of canine urinary bladder tumors [20]

T: Primary tumor	
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: Regional lymph node (RLN)	
N0	No evidence of RLN involvement
N1	RLN involved
N2	RLN and juxta RLN involved
M: Distant metastasis	
M0	No evidence of distant metastasis
M1	Distant metastasis detected

Materials and methods

Subjects and eligibility

This study was conducted at the Purdue University Veterinary Teaching Hospital following guidelines and approval of the Purdue Animal Care and Use Committee. Subjects for this study were privately owned pet dogs with naturally occurring, histopathologically confirmed TCC of the urinary bladder. Entry requirements for dogs in this study included: no prior cisplatin or piroxicam therapy, normal serum urea nitrogen (SUN) and creatinine concentrations, expected minimum survival of 6 weeks, and informed pet owner consent. With the exception of days when dogs were undergoing clinical evaluation and cisplatin treatment, the dogs lived at home with their owners.

Study design

This was a prospective, randomized clinical trial in pet dogs with TCC to determine whether cisplatin combined with piroxicam would induce remission of TCC more frequently than cisplatin alone. Dogs with TCC were randomized to receive either cisplatin alone or cisplatin plus piroxicam.

Clinical staging was performed prior to and at 6-week intervals during cisplatin or cisplatin/piroxicam therapy. Staging procedures included physical examination, thoracic and abdominal radiography, contrast cystography, and cystosonography as previously described [6]. Thoracic radiography included ventral-dorsal, left lateral, and right lateral projections. Abdominal radiography included ventral-dorsal and right lateral views. During contrast cystography, ventral-dorsal, dorsal-ventral, and right and left lateral projections were made. The clinical stage of each tumor was determined according to criteria established by the World Health Organization for canine bladder tumors (Table 1) [20].

Subject monitoring included a CBC, platelet count, serum biochemical profile, and urinalysis (including cytologic examination of urine sediment for malignant cells) prior to each cisplatin treatment, and a CBC and platelet count 10 days after each cisplatin treatment. Urine culture and sensitivity tests were performed when bacterial cystitis was detected on urinalysis. Permission to perform a necropsy was requested at the time of death.

Cisplatin was provided by Bristol Laboratories, Bristol-Myers Squibb Co., Princeton, N.J. Piroxicam was provided by Pfizer, New York, N.Y. Upon entry into the study, dogs were randomized to receive either cisplatin (60 mg/m^2 i.v. every 21 days) as previously described [5, 12], or cisplatin (60 mg/m^2 i.v. every 21 days) combined with piroxicam (0.3 mg/kg orally every 24 h). Briefly, diuresis was induced by administering 0.9% saline i.v. at a rate of 18 ml/kg per h for 4 h prior to and for 2 h after cisplatin administration. Cisplatin was administered i.v. over a 20-min period. Butorphanol (Torbugesic; 0.4 mg/kg i.v.; Fort Dodge Laboratories, Fort Dodge, Iowa) was given 30 min prior to cisplatin to decrease vomiting. Cisplatin therapy was delayed if the neutrophil count was $<3{,}000/mm^3$ (reference range 3,000–12,000/mm^3), if the platelet count was $<50{,}000/mm^3$ (reference range 200,000–900,000/mm^3), if the serum creatinine concentration was >2.0 mg/dl (reference range 0.5–1.5 mg/dl) or if the SUN concentration was >40 mg/dl (reference range 7–32 mg/dl) in the absence of gastrointestinal bleeding.

If therapy was delayed, laboratory tests were re-evaluated weekly, and cisplatin reinstituted when the neutrophil and platelet counts were normal and the serum creatinine concentration was <2.0 mg/dl. If the serum creatinine and SUN concentrations normalized, cisplatin was reinstituted at the original dose. If mild azotemia (serum creatinine 1.6–2.0 mg/dl, SUN 33–40 mg/dl) persisted, then cisplatin was reinstituted at a dose of 50 mg/m^2. If more severe azotemia persisted, then cisplatin therapy was discontinued. In addition, the dose of cisplatin was reduced by 20% if unacceptable myelosuppression (neutrophil count $<1{,}500/mm^3$ or platelet count $<50{,}000/mm^3$) was noted. If evidence of gastrointestinal irritation (anorexia, vomiting, melena) was observed, piroxicam was discontinued for 3–5 days or until clinical signs resolved, and was then reinstituted with misoprostol (Cytotec; 3 μg/kg every 8 h orally; G.D. Searle Co., Chicago, Ill.).

Tumor responses were defined as: complete remission (CR), the complete resolution of all clinical and radiographic evidence of tumor; partial remission (PR), ≥50% decrease in tumor volume with no new tumor lesions; stable disease (SD), $<50\%$ change in tumor volume and no new tumor lesions; and progressive disease (PD), ≥50% increase in tumor volume or the development of new tumor lesions. Treatment was scheduled to continue until two cisplatin doses had been given after documentation of CR, or until the development of PD, or unacceptable toxicity. In the cisplatin/piroxicam group, piroxicam was continued as maintenance therapy. When PD was noted in dogs in the cisplatin/piroxicam therapy group, alternative therapy was offered off study. When PD occurred in the cisplatin alone treatment group, dogs were then treated with piroxicam alone to determine whether piroxicam would have activity in cisplatin-resistant TCC.

Information collected on each dog included: tumor response at 42 days, maximum tumor response, time to failure (time from the start of therapy until PD or death if PD had not occurred at death), survival time (measured from the beginning of therapy until death), serum biochemical evidence of renal toxicity, clinical signs of gastrointestinal toxicity, and evidence of myelosuppression. Criteria used to classify renal, hematologic, and gastrointestinal toxicity are listed in Table 2. If there was evidence of gastrointestinal irritation (gross melena, positive fecal occult blood test) which could cause an increase in SUN, renal toxicity was defined using serum creatinine concentration alone, and not SUN concentration. Evidence of gastrointestinal toxicity was recorded for the first 48 h following cisplatin treatment (time of cisplatin-induced vomiting) and for other treatment days.

Table 2 Classification of renal, hematologic, and gastrointestinal toxicity

Toxicity	None	Mild	Moderate	Severe
Renal				
Serum urea nitrogen[a] (mg/dl)	7–32	33–40	41–70	>70
Serum creatinine (mg/dl)	0.5–1.5	1.6–2.0	2.1–3.5	>3.5
Gastrointestinal				
Days of anorexia	0	≤1	2–3	>3
Episodes of vomiting	0	1–2	>2	Uncontrolled
Melena	No	No	Yes	Yes
Episodes of diarrhea	0	1–2	>2	Uncontrolled
Supportive care needed	No	No	Yes	Yes
Hospitalization needed	No	No	No	Yes
Hematologic				
Neutrophils ($\times 10^3/mm^3$)	3–12	2–2.9	1–1.9	<1
Platelets ($\times 10^3/mm^3$)	200–900	100–199	50–99	<50

[a] If there was evidence of gastrointestinal hemorrhage (which could increase the serum urea nitrogen independent of renal function), then creatinine concentration alone was used to classify the renal toxicity

Statistical analyses and sample size calculation

To detect a 30% difference between treatment groups in the percentage of dogs that achieved remission, it was calculated that 30 dogs would be needed in each treatment group. This sample size calculation was made with a power of 0.8, with a projected remission rate of 20% for cisplatin, and with $P < 0.05$ being significant. In case the difference in remission rate between treatment groups was greater than 30%, interim statistical analyses were scheduled to be performed after 8, 16, and 24 dogs had been enrolled in each treatment group. To terminate the trial after interim analyses, a P-value of <0.01 was required.

Data were coded and entered into a computerized database using Epi Info version 6.03 [10]. Statistical analyses were performed using SAS System for Windows version 6.11 [23] and BMDP New System for Windows version 1.1 [1]. A P-value of <0.05 was considered significant for all analyses, except for the difference in remission rate in interim analyses ($P < 0.01$ required). For statistical analysis of categorical variables, a Fisher's Exact test and Wilcoxon test were used due to expected cell sizes less than five. For categorical variables that had more than two groups, a Pearson Chi-squared was used. Nonparametric tests were used for statistical analysis of continuous variables, because they were not normally distributed. The two treatment groups were compared for differences in age, weight, gender, TNM stage, urethral involvement, prostate involvement, initial SUN and creatinine, number of cisplatin doses, gastrointestinal, hematologic and renal toxicity, tumor response, time to failure, and duration of survival.

Results

Subject characteristics are summarized in Table 3. There were no significant differences between the two treatment groups in regard to gender, age, weight, breed, TNM stage, urethral involvement, prostate involvement, or initial SUN and serum creatinine concentrations. After eight dogs had been treated and evaluated in each treatment group, a significant difference in frequency of remission was noted. The tumor responses in dogs treated with cisplatin/piroxicam were: two CR, four PR, two SD and no PD. The tumor responses in dogs treated with cisplatin alone were: no CR, no PR, four SD, and four PD (Fisher's Exact test, $P < 0.004$). The randomization process was stopped at this point. Six additional dogs were subsequently entered in the cisplatin/piroxicam group, and the tumor responses were no CR, four PR, two SD and no PD. The overall remission rate of 71% (10 of 14 dogs) remained significantly different than the remission rate (0 of 8 dogs) with cisplatin (Fisher's Exact test, $P < 0.002$). The remissions in the cisplatin/piroxicam group included PR in two dogs with nodal metastasis and PR in one dog with distant metastasis.

Dogs treated with cisplatin alone received a mean of 2.9 (range 2–4, median 3) cisplatin doses, while dogs receiving cisplatin/piroxicam received a mean of 3.8 (range 2–6, median 3.5) doses of cisplatin ($P > 0.2$). As discussed below, cisplatin therapy was withdrawn frequently in the cisplatin/piroxicam treatment group due to renal toxicity. In two dogs that had CR with cisplatin/piroxicam, cisplatin was withdrawn at the time of CR (rather than after two additional doses as originally planned) due to renal toxicity. Both dogs had relapse of their tumors at 120 and 250 days, respectively. Time to failure (time from first cisplatin treatment until PD or death) ranged from 42 to 151 days (median 84 days) in the cisplatin alone group, and from 46 to 259 days (median 124 days) in the cisplatin/piroxicam group (Kruskal-Wallis analysis of variance, $P < 0.07$).

When PD was documented in dogs treated with cisplatin alone, cisplatin was discontinued and piroxicam (alone) was instituted. Tumor responses to piroxicam alone in these dogs were: no CR, two PR, five SD, and one PD. The survival in the cisplatin-alone (followed by piroxicam alone) treatment group (median 309 days, range 140–518 days) was not significantly different from the survival (median 246 days, range 46–810 days) in the combined therapy group ($P < 0.5$).

Renal toxicity was noted in 4 of 8 dogs receiving cisplatin alone and in 12 of 14 dogs treated with cisplatin/piroxicam (Fishers Exact test, $P < 0.14$) with most dogs having moderate renal toxicity (Table 4). After treatment with cisplatin alone or cisplatin/piroxicam,

Table 3 Subject and tumor characteristics

	Cisplatin	Cisplatin/piroxicam
Number of dogs	8	14
Age (years)		
Median	9.5	12
Range	9–16	8–15
Gender		
Intact male	1	0
Neutered male	1	3
Intact female	0	0
Neutered female	6	11
Breed		
Pure breed	7	9
Mixed breed	1	5
Weight (kg)		
0–15	4	5
15–30	3	7
>30	1	2
TNM		
T2N0M0	6	8
T2N1M0	1	3
T2N0M1	1	2
T3N1M0	0	1
Urethral involvement		
Yes	5	12
No	3	2
Prostate involvement		
Yes	0	1
No	8	13

dogs had a mean serum creatinine concentration of 1.8 ± 1.2 mg/dl and 2.0 ± 0.6 mg/dl, respectively. After cisplatin or cisplatin/piroxicam treatment, dogs had mean SUN concentration of 37.6 ± 32.3 mg/dl and 49.7 ± 16.2 mg/dl, respectively. Data from dogs with evidence of gastrointestinal hemorrhage (which could increase the SUN-independent of renal function) were excluded when calculating these mean SUN concentrations. Renal toxicity was not associated with age, weight, gender, initial SUN and creatinine concentrations, treatment group, number of cisplatin doses, treatment response, TNM stage, presence of urethral or prostate involvement, or concurrent gastrointestinal or hematologic toxicity. Renal toxicity resulted in alteration in the treatment protocol in 10 of 14 dogs (71%) in the cisplatin/piroxicam therapy group and in 1 of 8 dogs (12.5%) treated with cisplatin alone (Table 4). Gastrointestinal and hematologic toxicities were generally mild (Table 4).

The cause of death or reason for euthanasia in dogs treated with cisplatin was TCC within the bladder/urethra in two dogs, metastatic TCC in two dogs, and nontumor-related causes in four dogs. For dogs treated with cisplatin/piroxicam, the cause of death or euthanasia was TCC within the bladder/urethra in seven dogs, metastatic TCC in three dogs, nontumor-related causes in two dogs, and unknown cause in two dogs.

Post-mortem examination was performed on seven dogs in the cisplatin alone treatment group and on eight dogs in the cisplatin/piroxicam group. TCC was found in the bladder in all dogs. Metastasis to regional lymph nodes was detected in two dogs in the cisplatin treatment group and in four dogs in the cisplatin/piroxicam treatment group. Distant metastasis was found in four dogs in the cisplatin-alone treatment group and in three dogs in the cisplatin/piroxicam treatment group. Histopathologic findings in the kidneys were similar between treatment groups and included membranous glomerulopathy (seven dogs), glumerulosclerosis (two dogs), glomerulonephritis (four dogs), chronic interstitial nephritis (nine dogs), hydronephrosis (two dogs), renal tubular atrophy (one dog), renal tubular nephrosis (one dog), fibrosis (five dogs), pyelonephritis (three dogs), papillary necrosis (one dog), and renal TCC (two dogs).

Table 4 Treatment toxicity (as defined in Table 2) and change in cisplatin therapy due to renal toxicity

	Treatment group	
	Cisplatin (n = 8)	Cisplatin/piroxicam (n = 14)
Gastrointestinal toxicity (within 48 h of cisplatin/>48 h post-cisplatin)		
None	5/5	7/5
Mild	2/2	5/7
Moderate	1/0	2/1
Severe	0/1	0/1
Hematologic toxicity		
None	5	9
Mild	1	3
Moderate	0	0
Severe	2	2
Renal toxicity		
None	4	2
Mild	1	3
Moderate	2	8
Severe	1	1
Change in therapy due to renal toxicity		
Cisplatin delayed	1	7
Cisplatin dose reduced	1	2
Cisplatin discontinued prematurely	1	10

Discussion

The purpose of this clinical study was to determine whether cisplatin combined with piroxicam would induce remission more frequently than cisplatin alone in a canine model [16] of human invasive urinary bladder cancer. Cisplatin/piroxicam did induce remission more frequently, but was also associated with dose-limiting renal toxicity. When a significant difference in remission rate was observed between the two treatment groups, the randomization process was stopped. Additional dogs were treated with cisplatin/piroxicam to better characterize the response to this treatment. The trial was discontinued after six additional dogs had been enrolled due to the high rate of renal toxicity. It is not known why none of the eight dogs treated with cisplatin had remission. Previous studies suggest that cisplatin induces remission in 12–20% of dogs with TCC [5, 12, 16].

The antitumor activity of cisplatin/piroxicam (71% remission rate) in a typically resistant solid tumor such as canine invasive TCC is an important finding. In canine TCC, the remission rate with either cisplatin alone or piroxicam alone has previously been reported to be ≤20% with median survival times of 130 and 180 days, respectively [5, 14]. Dogs in this phase III clinical trial treated with cisplatin/piroxicam had a median survival of 246 days, and dogs treated with cisplatin alone (followed by piroxicam alone) had a median survival of 309 days. In the Purdue Comparative Oncology Program Tumor Registry [17], the median survival time of 42 dogs with localized TCC that underwent surgery alone (surgical resection or debulking) was only 106 days (unpublished data, D. Knapp). In previous studies the median survival times were 130 days for cisplatin alone and 180 days for piroxicam alone [5, 14]. Therefore, it appears that both treatment groups in this study had improved survival. While this was expected in the dogs receiving cisplatin/piroxicam with the increased remission rate, the length of survival in the dogs treated with cisplatin alone followed by piroxicam alone was not expected to be this long. The small number of dogs in the clinical trial, however, must be considered in interpreting survival data.

Renal toxicity was dose-limiting in dogs receiving cisplatin/piroxicam in this trial and precluded the administration of the planned number of cisplatin doses. The authors acknowledge that a conservative approach was taken in this trial with regard to continuing cisplatin therapy in the presence of azotemia. For most owners of pet dogs, the quality of their pet's life is the most important issue. Cisplatin therapy was often discontinued to prevent the possibility of more severe kidney dysfunction which could decrease the quality of life. Renal toxicity was not surprising with this drug combination. Cisplatin is a direct nephrotoxic agent; it first affects proximal tubules, followed by distal tubules, and alters renal blood flow and glomerular filtration rate [8]. Piroxicam and other cox inhibitors can interfere with renal blood flow by inhibition of prostaglandin synthesis [25]. Neither tubular necrosis, suggestive of cisplatin toxicity, nor renal papillary necrosis suggestive of cox inhibitor toxicity, were consistent findings on post-mortem examination [8, 25]. Multiple lesions in the kidneys, however, could have masked changes indicative of cisplatin or piroxicam nephrotoxicity.

Regardless of the conservative nature of this trial, it is clear that strategies need to be investigated to prevent or limit the renal toxicity of cisplatin/piroxicam therapy before it is evaluated in human clinical trials and before recommending it routinely in dogs with TCC. The antitumor activity of cisplatin/piroxicam is great enough to warrant investigation of strategies to overcome the renal toxicity while maintaining antitumor effects. If renal protective strategies can be developed that allow optimal cisplatin dosages to be given, the cisplatin/piroxicam combination may prove even more effective, inducing more durable and complete remissions, against TCC than in this study. Multiple strategies could be investigated to prevent the renal toxicity of cisplatin/piroxicam. Agents that have been reported to reduce the renal toxicity of cisplatin include hypertonic saline, sodium thiosulfate, amifostine, diethyldithiocarbamate, and others [2, 4]. These agents may be useful in reducing the renal toxicity of cisplatin/piroxicam. Alternatively, investigations could be performed in which carboplatin [6, 24] is substituted for cisplatin, or a cyclooxygenase-2 inhibitor [9] is substituted for piroxicam.

The mechanisms of the improved antitumor activity observed in this study with cisplatin/piroxicam are unknown. At concentrations achievable in vivo, no in vitro cytotoxicity of piroxicam or other cox inhibitors has been detected against four canine tumor cell lines [15], or against human bladder cancer cell lines (unpublished data, D. Knapp). In both canine and human cell lines, direct cytotoxicity by cox inhibitors occurs at concentrations much higher than would be achieved in vivo [15, 21]. Other mechanisms that may be involved include effects on: immune function, apoptosis, and angiogenesis [7, 11, 27]. Other possible mechanisms of enhanced antitumor effects could include changes in cisplatin pharmacokinetics and increased cisplatin concentration, or modulation of cisplatin resistance.

In conclusion, cisplatin/piroxicam had marked antitumor activity against naturally occurring canine TCC, a relevant model of human invasive TCC. Prior to clinical trials of cisplatin/piroxicam in humans, strategies to prevent renal toxicity, while preserving antitumor activity, must be developed.

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