Carboplatin and piroxicam therapy in 31 dogs with transitional cell carcinoma of the urinary bladder

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Abstract

Invasive transitional cell carcinoma (TCC) of the urinary bladder responds poorly to medical therapy. Combining platinum chemotherapy with a cyclooxygenase (cox) inhibitor has shown promise against canine TCC, where the disease closely mimics the human condition. A phase II clinical trial of carboplatin combined with the cox inhibitor, piroxicam, was performed in 31 dogs with naturally occurring, histopathologically confirmed, measurable TCC. Complete tumour staging was performed before and at 6-week intervals during therapy. Tumour responses in 29 dogs included 11 partial remissions, 13 stable disease and five progressive disease. Two of the 31 dogs were withdrawn prior to the re-staging of the tumour. Gastrointestinal toxicity was observed in 23 dogs. Hematologic toxicity was noted in 11 dogs. The median survival was 161 days from first carboplatin treatment to death. In conclusion, carboplatin/piroxicam induced remission in 40% of dogs providing evidence that a cox inhibitor enhances the antitumour activity of carboplatin. The frequent toxicity and limited survival, however, do not support the use of this specific protocol against TCC.

Keywords
animal model, carboplatin, cox inhibitor, piroxicam, urinary bladder cancer

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Introduction

More than 14 000 people die from invasive urinary bladder cancer each year in the United States.[1] Most deaths are due to invasive transitional cell carcinoma (TCC) which has metastasized to distant organs and is resistant to chemotherapy.[1] If the efficacy of chemotherapy for invasive bladder cancer could be improved, the mortality from this disease would be reduced.

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Studies of pet dogs with TCC are conducted in order to develop more effective treatment to benefit the dogs and to generate information leading to more effective treatment strategies to study in humans with TCC. Investigators in the Purdue Comparative Oncology Program have studied the effects of cisplatin in naturally occurring invasive TCC in pet dogs in which the disease closely mimics the human condition.[2–4] In studies in pet dogs, a cyclooxygenase (cox)-inhibiting drug, piroxicam, given in combination with cisplatin was much more effective (70% remission rate) than

either drug given alone ($\leq$20% remission rate).[4] This finding is important as cisplatin is one of the most active chemotherapeutic agents for invasive TCC.[1] Unfortunately, the combination of cisplatin and piroxicam caused unacceptable renal toxicity.[4] Cisplatin directly damages renal tubule epithelial cells.[5] and non-selective cox-inhibiting drugs like piroxicam can interfere with renal blood flow.[6]

Carboplatin [diamine(1,1-cyclobutanedicarboxylato)-platinum(II)], a cisplatin analogue associated with much less renal toxicity than cisplatin, has been reported to have antitumour activity in humans with TCC.[7,8] Carboplatin has also been evaluated in pet dogs with TCC.[9] The drug has been well tolerated by pet dogs when dosed appropriately, although the antitumour activity appears less than that with cisplatin.[9] We postulated that piroxicam would enhance the antitumour activity of carboplatin and that carboplatin/piroxicam would not be associated with the renal toxicity of cisplatin/piroxicam. The purpose of this prospective study was to determine the antitumour activity and toxicity of carboplatin/piroxicam in dogs with naturally occurring invasive TCC.

Materials and methods

This study was approved by the Purdue Animal Care and Use Committee. Entry requirements for the study included pet dogs with naturally occurring, histopathologically confirmed, measurable TCC of the urinary bladder; serum creatinine concentration of $\leq$3 mg dL^{-1}; failure of any prior cancer therapy; and informed pet owner consent. The study was conducted following Gehan's two-stage phase II clinical trial design.[10]. According to the design, if a drug has an activity rate (percentage of cases undergoing remission) of 20% or greater, at least one subject in the first 14 entered into the study would be expected to have remission (95% confidence). If one or more remissions are observed in the first 14 subjects treated, additional cases are enrolled. If none of the first 14 subjects has remission, the trial is stopped.

Tumour staging, performed before and at 6-week intervals during therapy, included thoracic radiography (right and left lateral and ventrodorsal views), abdominal radiography (right lateral and ventrodorsal views), abdominal ultrasonography, contrast cystography and cystosonography similar to that previously reported.[9] The tumour stage was determined according to the World Health Organization TNM classification.[11] A CBC, platelet count, BUN and serum creatinine were evaluated prior to each carboplatin treatment. CBC and platelet counts were performed 7–10 days after each carboplatin treatment.

Piroxicam (Pfizer, New York, NY, USA) was given at a dosage of 0.3 mg kg^{-1} every 24 h starting at the time of carboplatin treatment. Carboplatin (Bristol Laboratories, Bristol-Myer Squibb Co., Princeton, NJ, USA) was administered at a dosage of 300 mg m^{-2} intravenously over 10 min every 3 weeks, or at a lower dose in dogs with renal compromise. The dosage of carboplatin was reduced as described in Table 1 if azotemia or ultrasound findings of marked bilateral hydronephrosis were present.

Tumour responses were defined as follows: complete remission (CR), complete resolution of all clinical, radiographic or ultrasonographic evidence of tumour; partial remission (PR), $\geq$50% reduction in tumour volume and no new tumour lesions; stable disease (SD), $<$50% change in tumour volume and no new tumour lesions; or progressive disease (PD), $\geq$50% increase in tumour volume or the development of new tumour lesions. Dogs with remission or stable disease remained on therapy, while dogs with progressive disease stopped receiving carboplatin/piroxicam therapy. Therapy was continued until two dosages of carboplatin were given after CR or until PD or unacceptable toxicity was noted.

Length of remission was defined as the time from the first day of treatment until relapse. Survival was defined as the time from the first day of treatment until death. Information recorded relating to drug toxicity included: evidence of renal toxicity (rise in serum creatinine), clinical signs of gastrointestinal toxicity and

Table 1. Criteria used for reducing the dosage of carboplatin in dogs with transitional cell carcinoma

Serum creatinine*	Carboplatin dosage†
$\leq$1.2 mg dL^{-1}	300 mg m^{-2}
1.3–2.2 mg dL^{-1}	250 mg m^{-2}
2.3–3.0 mg dL^{-1}	200 mg m^{-2}

*Reference range for canine serum creatinine is 0.5–1.5 mg dL^{-1}.
†In dogs with ultrasound findings of bilateral hydronephrosis, the dosage of carboplatin was further reduced by 50 mg m^{-2}.

evidence of haematologic toxicity (as determined by CBC and platelet count) (Table 2).

All data analyses were performed with standard statistical software (SAS Institute, Cary, NC, USA), and differences were considered to be statistically significant at $P < 0.05$. Tumour response (remission versus stable and/or progressive disease) was compared with respect to age, weight, gender, urethral involvement, prostatic involvement, gastrointestinal toxicity, renal toxicity, bone marrow suppression, TNM stage and whether or not surgery was performed before the dog entered the clinical trial. Weight was analysed to determine whether there was an association between the dog's initial weight and whether or not a dog experienced renal toxicity and/or gastrointestinal toxicity after treatment with carboplatin/piroxicam. Categorical variables were compared using a Fisher's exact test or Chi-square analysis. Continuous variables were compared using a Wilcoxon two-sample test. Proportional hazards regression was used to determine whether there was an association between age, weight and number of doses of carboplatin/piroxicam with survival. Kaplan–Meier survival analyses were performed to determine whether there was a significant difference in survival associated with gender, whether or not surgery was performed, urethral involvement of the tumour, prostatic involvement of the tumour, tumour response (remission versus stable and/or progressive disease), renal toxicity, gastrointestinal toxicity, bone marrow suppression and TNM.

Results

Following evaluation of the first 14 dogs enrolled, five dogs had remission, thus justifying continuation into the second phase of the study. Thirty-one dogs total were included in the study, including 19 spayed females and 12 neutered males. There were seven Shetland sheepdogs, six mixed-breed dogs, three beagles, four Scottish terriers and one each of the following breeds: Staffordshire bullterrier, miniature schnauzer, Welsh corgi, Airedale, Labrador retriever, Maltese, Lhasa apso, Dalmatian, Shih-Tzu and Wheaten terrier in the study. The median weight of dogs was 14.4 kg [32 lb; range 3.6–47 kg (8–103 lb)]. Median age of dogs at entry into the study was 11 years (range 6–15 years). Information on tumour location and stage is summarized in Table 3.

Of the 31 dogs in the study, 21 dogs received an initial carboplatin dosage of 300 mg m^{-2} and 10 dogs received a lower dosage (250 mg m^{-2}, $n = 3$; 200 mg m^{-2}, $n = 6$; 150 mg m^{-2}, $n = 1$). The mean carboplatin dosage per dog was 210 mg m^{-2}. The mean and median number of carboplatin treatments given per dog was 4. Six dogs had received prior therapy with piroxicam ($n = 4$), cisplatin/piroxicam ($n = 4$), mitoxantrone

Table 2. Classification of renal, haematologic and gastrointestinal toxicity

	Mild	Moderate	Severe
Renal			
Serum creatinine (mg dL^{-1})	1.6–2.0	2.1–3.5	>3.5
Gastrointestinal			
Episodes of vomiting/diarrhoea	1–2	>2	Uncontrolled
Supportive care needed	No	Yes	Yes
Hospitalization needed	No	No	Yes
Haematologic			
Neutrophils ($\times$10 mm^{-3})	2–2.9	1–1.9	<1
Platelets ($\times$10 mm^{-3})	100–199	50–99	<50

Table 3. TNM stage (WHO classification, 11) of urinary bladder transitional cell carcinoma in dogs treated with carboplatin/piroxicam

TNM stage*	Number of dogs
$T_2N_0M_0$	24
$T_2N_1M_0$	2
$T_2N_0M_1$	2
$T_3N_0M_0$	1
$T_3N_1M_1$	2
Urethra involved	21
Prostate involved	4

*The WHO TNM staging system for canine urinary bladder tumours differs from the WHO TNM staging system for human urinary bladder tumours. In the canine system, T_1 lesions are superficial, T_2 lesions invade into the bladder wall and T_3 lesions extend beyond the bladder wall.

($n = 1$), doxorubicin ($n = 1$) and actinomycin D ($n = 1$) before entering the study. Ten dogs received other therapies after failing carboplatin/piroxicam (piroxicam, $n = 5$; cisplatin, $n = 2$; cisplatin/piroxicam, $n = 2$; gemcitabine, $n = 1$; and cyclophosphamide, $n = 1$).

Tumour response was evaluated in 29 dogs. Two of the 31 dogs in the study were withdrawn prior to the re-staging of the tumour following treatment. One dog experienced severe gastrointestinal toxicity and the pet owner withdrew the dog from the study prior to re-staging. A second dog developed hind limb weakness, and the pet owner did not return the dog for further evaluation. None of the dogs experienced CR. Of the 29 dogs evaluated for tumour response, 11 dogs had PR, 13 dogs had SD and five dogs had PD. Tumour response was not associated with age, weight, gender, urethral involvement of the tumour, prostatic involvement of the tumour, gastrointestinal toxicity, renal toxicity, bone marrow suppression, TNM stage or whether or not surgery was performed prior to entering the study. The median survival was 161 days from first carboplatin treatment to death (Fig. 1) and 196 days from diagnosis to death. Survival was negatively associated with advanced TNM stage ($P < 0.001$) and with prostatic involvement of the tumour. Survival in 27 dogs without prostatic involvement (228 days) was significantly longer ($P < 0.001$) than survival in four dogs with prostatic involvement of the tumour (70.5 days).

Of the 31 dogs included in the study, gastrointestinal toxicity was observed in 23 dogs with toxicity being mild in five dogs, moderate in 10 dogs and severe (requiring hospitalization) in eight dogs. The gastrointestinal toxicity included vomiting in 12 dogs, diarrhoea in nine dogs, anorexia in 18 dogs and melena in two dogs. Symptomatic care (including intravenously fluids, antiemetics and gastrointestinal protectants) was instituted as considered appropriate. There was no significant association between gastrointestinal toxicity and initial weight or serum creatinine. Hematologic toxicity (consisting of neutropenia and/or thrombocytopenia) was noted in 11 dogs, with toxicity being mild in four dogs, moderate in four dogs and severe in three dogs. Six dogs had

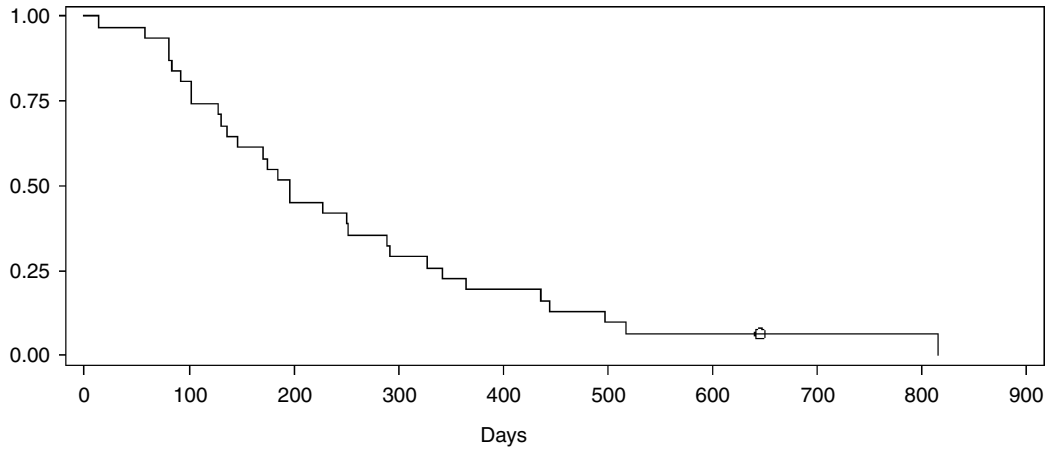

Figure 1. Kaplan–Meier survival curve for 31 dogs with transitional cell carcinoma treated with carboplatin/piroxicam.

neutropenia and normal platelet counts and five dogs had neutropenia and thrombocytopenia. Renal toxicity was not observed in any of the dogs. Similarly, the serum creatinine concentration did not increase while the dogs were on therapy.

Discussion

The subject and tumour characteristics for this study were similar to those reported previously for dogs with TCC.[3,9,12] The median age of dogs in the study was 11 years and female dogs comprised 61% of the study subjects. Similarly, the association noted between advanced TNM stage or prostatic involvement of the cancer and reduced survival has been observed in other studies.[3]

The purpose of this study was to determine the antitumour activity and toxicity of carboplatin when combined with piroxicam in dogs with naturally occurring invasive TCC. The results of the study provide evidence for two major conclusions. First, the study results provide evidence that combining a cox inhibitor with carboplatin is more effective than either drug alone and that the beneficial effect appears more than additive. The remission rate in this study (40%) with carboplatin/piroxicam was considerably higher than that reported with carboplatin alone (<10%)[9] and with piroxicam alone (18%).[3,13] It is not possible to know whether the piroxicam enhanced the effects of the carboplatin or whether the carboplatin enhanced the effects of the piroxicam, just that the combination resulted in a favourable remission rate.

The second major conclusion from the study is that the specific carboplatin/piroxicam protocol used in this study does not appear to be an optimal treatment for canine TCC. There were no complete remissions, and partial remissions associated with carboplatin/piroxicam were often of short duration. Survival was also short in several dogs. The median survival of 161 days did not appear longer than that of dogs treated with piroxicam alone (195 days) in previous studies (3). Toxicity was also frequent in this study, especially gastrointestinal toxicity.

The finding that remission with carboplatin/piroxicam was not as frequent as that with cisplatin/piroxicam was not entirely unexpected since the efficacy of single-agent carboplatin against canine TCC appears less than that of cisplatin and some other chemotherapies.[3] Similarly, in humans with TCC, carboplatin has appeared less effective than cisplatin.[14,15]

Toxicity was frequent in dogs in this study. Although renal toxicity was not noted, bone marrow suppression and gastrointestinal toxicity were common. Bone marrow suppression, including frequency (35% of dogs) and severity (toxicity being moderate-to-severe in 63% of dogs with toxicity), was similar to that reported for single-agent carboplatin.[9] Gastrointestinal toxicity, however, appeared more frequent in dogs receiving carboplatin/piroxicam than in dogs previously treated with carboplatin alone[9] or piroxicam alone.[3,13] Gastrointestinal toxicity was noted in 23 of 31 dogs (74%) receiving carboplatin/piroxicam, and the toxicity was moderate-to-severe in 78% of the dogs with gastrointestinal side-effects. Eight of the dogs with gastrointestinal toxicity required hospitalization.

The frequency and severity of toxicity associated with carboplatin/piroxicam along with the short duration of remission and short survival demonstrate that this specific protocol is not optimal for dogs with TCC. This does not mean, however, that this protocol and other protocols combining cox inhibitors and chemotherapy should be abandoned altogether. More aggressive strategies could be employed in an attempt to reduce gastrointestinal toxicity to make the protocol more tolerable. Also, it is possible that carboplatin/piroxicam may be more effective and better tolerated in dogs without bladder cancer, i.e. in dogs with other cancers, but normal kidneys and urinary tract. TCC can cause renal insufficiency (due to partial urinary obstruction or chronic secondary infection), and this would lead to reduced carboplatin excretion and to more toxic concentrations of the drug in the body. In this study, renal function was assessed by serum creatinine concentration. The authors recognize that determination of glomerular filtration rate by creatinine clearance or nuclear

scintigraphy is a more sensitive measure of renal function, and that creatinine clearance is used to determine carboplatin dosing in humans.[16] Recently, creatinine clearance has been used to predict carboplatin clearance in cats.[17] Creatinine clearance was not used in this canine study because of the risks associated with urinary catheterization (which is typically performed to measure urine volume in creatinine clearance studies in dogs). When the TCC weakens the wall of the bladder or urethra, there is a risk of penetrating and tearing the wall of the urinary tract when passing a catheter. In addition to possible impaired kidney function resulting from the tumour, it is also possible that piroxicam treatment caused a reduction in renal blood flow in some dogs. Cox-inhibiting drugs are known to block production of prostaglandins in the afferent and efferent arterioles and to contribute to reduction in renal blood flow.[6] Therefore, it is possible that kidney function was less than normal in some dogs even when the serum creatinine concentrations were normal. If this were the case, higher concentrations of carboplatin could have been present in the dogs, and this could have contributed to the gastrointestinal toxicity.

Although the results of this study provide evidence that cox-inhibiting drugs may be used to enhance the efficacy of chemotherapy against TCC, the precise combination of drugs and treatment protocol remains to be defined. Henry *et al.*[12] reported remission in 35% of dogs with TCC treated with mitoxantrone/piroxicam. In a randomized study, cisplatin/piroxicam induced remission in 70% of dogs with TCC, but renal toxicity was greater than desired.[4] While carboplatin/piroxicam failed to result in durable remission or survival in most dogs, it may be reasonable to evaluate a cox inhibitor in combination with carboplatin plus other chemotherapeutic agents. Carboplatin combined with paclitaxel, for example, has been reported to be efficacious in humans with invasive TCC,[18] and it is possible that the addition of a cox inhibitor to this type of protocol would prove even more beneficial.

A major question that remains to be answered regarding cox inhibitor/chemotherapy treatment protocols is whether to use a non-selective cox inhibitor like piroxicam (which inhibits the enzyme activity of both cox-1 and cox-2) or to use a selective cox-2 inhibitor. Cox-2 is expressed in the majority of invasive TCC in humans and dogs, but not in the normal bladder epithelium.[19–21] Cox-1 is expressed in normal and cancerous urothelial cells.[19,20] Cox-2 is thought to play a major role in the development and progression of urinary bladder cancer and to serve as a target for therapy.[22] Cox-2 inhibitors have become available which are associated with less gastrointestinal toxicity than non-selective cox inhibitors. Collectively, this information has strongly supported the evaluation of selective cox-2 inhibitors as anticancer agents. Recently, however, it has become apparent that selective cox-2 inhibitors can have adverse cardiovascular effects in humans.[23,24] This has led to widespread concern regarding the use of selective cox-2 inhibitors. Studies must be carefully conducted to determine the risk/benefit ratio for the use of cox-2 inhibitors in cancer patients. It is likely that carefully prescribed cox-2-inhibitor treatment may result in beneficial effects such as increasing the frequency and duration of remission, prolonging survival and improving the quality of life. Such beneficial effects, if they occur, would justify the use of cox-2 inhibitors in the treatment of cancer. If the risk of dying from a specific form of cancer exceeded the risk of death from dying of that cancer while receiving cox-2-inhibitor treatment, then cox-2-inhibitor treatment could be considered appropriate.

In our study of carboplatin/cox-inhibitor treatment in dogs with TCC, the non-selective cox inhibitor, piroxicam, was used. Piroxicam was selected because: (i) this drug had been associated with anticancer effects against canine TCC when given as a single agent.[3,13] (ii) piroxicam had enhanced the effects of another platinum chemotherapy.[4] and (iii) selective cox-2 inhibitors for use in dogs were not available when the study was initiated. Although the vast majority of studies indicate that cox-2 is the most important cox isoform in cancer development and progression, a limited number of studies suggest an important role for cox-1 as well.[25,26] If inhibition of cox-1

contributes to the antitumour activity of non-selective cox inhibitors, then these non-selective agents (which block cox-1 and cox-2 activity) may have an advantage over selective cox-2 inhibitors.

In conclusion, the combination of carboplatin/piroxicam induced remission in 40% of dogs with TCC demonstrating that a cox inhibitor can enhance the antitumour activity of carboplatin. The specific carboplatin/piroxicam protocol used, however, was not found to be optimal due to short duration of remission and survival, and frequent toxicity. This does not indicate that chemotherapy/cox-inhibitor treatment protocols should be abandoned. In contrast, improving the remission rate from <10% (carboplatin alone) to approximately 40% (carboplatin/piroxicam) generates enthusiasm for further study of chemotherapy/cox-inhibitor treatment. Cox inhibitors may play a very important role in enhancing the antitumour effects of chemotherapy. Further studies are crucial to define the optimal combination of chemotherapy and cox-inhibitor treatment.

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