Clinical Evaluation of Mitoxantrone and Piroxicam in a Canine Model of Human Invasive Urinary Bladder Carcinoma[1]

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ABSTRACT

Purpose: Cyclooxygenase inhibitors show promise in chemoprevention and therapy of certain carcinomas, an effect that may be additive to that of standard chemotherapy. The purpose of this study was to evaluate the efficacy of combined therapy using the cyclooxygenase inhibitor, piroxicam, and mitoxantrone against a relevant canine model of human invasive bladder cancer.

Experimental Design: Fifty-five dogs with transitional cell carcinoma of the urinary bladder were enrolled in this nonrandomized one-armed prospective multi-institutional clinical trial. Mitoxantrone was administered i.v. (5 mg/m^2) every 21 days for four treatments, and piroxicam was administered p.o. (0.3 mg/kg/day) for the study duration. Tumor staging was performed at baseline, day 42 and every 3 months after protocol completion. Endpoints included time-to-treatment failure and survival time (ST).

Results: Response data were available for 48 dogs and included one complete response, 16 partial responses, 22 with disease stabilization, and 9 with progressive disease for an overall 35.4% measurable response rate. Subjective improvement occurred in 75% of treated dogs. Median time-to-treatment failure and ST were 194 and 350 days, respectively. Using censoring and end point definitions similar to those of previous reports of dogs treated with piroxicam alone, the median ST in this study was 291 days, compared with 181 days with piroxicam alone. Diarrhea and azotemia were the most common treatment complications.

Conclusions: Mitoxantrone/piroxicam induced remission more frequently than previously reported for either drug as a single agent in this canine model of invasive human transitional cell carcinoma. Additional evaluation of these drugs in combination protocols should be explored.

INTRODUCTION

Bladder cancer accounts for >54,000 new cancer cases in the United States each year (1). The role of chemotherapy, primarily in the neoadjuvant setting, has been evaluated in several prospective clinical trials. Preliminary data from the Southwest Oncology Group-based Intergroup trial indicates a significant survival benefit with neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (2). The combination of paclitaxel and gemcitabine has also shown promise for the treatment of advanced bladder cancer (3, 4). Despite these advances, >12,000 deaths attributable to bladder cancer were anticipated in the United States in 2001, making this one of the top 10 causes of cancer deaths among men (1). Clearly, more effective therapy is needed for invasive TCC[5] of the urinary bladder. Strategies to enhance the efficacy of chemotherapy and prevent metastasis may lead to a decreased mortality rate.

Canine TCC of the bladder is a naturally occurring disease, which serves as a relevant model of human invasive TCC (5). Similar features of the tumor between the two species include histopathological characteristics, biological behavior, molecular features, response to medical therapy, and prognosis. As such, results of clinical trials in dogs with bladder TCC may have direct application to treatment of the disease in people. A standard of care chemotherapy protocol for treatment of canine TCC had not been established. Treatment protocols that have been investigated in dogs with TCC include cisplatin, carboplatin, and the COX inhibitor, piroxicam, used as single agents, as

[5] The abbreviations used are: TCC, transitional cell carcinoma; COX, cyclooxygenase; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; TTF, time to treatment failure; GI, gastrointestinal.

well as combinations of doxorubicin and cyclophosphamide, cisplatin and piroxicam, and carboplatin with piroxicam. Median survival times achieved with single agent therapy have ranged from 130 to 181 days and those of combination protocols have ranged from 93 to 259 days (6–12). Results of recent canine clinical trials have suggested that piroxicam improves response rates to platinum-based chemotherapy for TCC of the bladder, but nephrotoxicity has been a concern with use of these protocols (5, 10, 11). The fact that expression of COX-2 was found in canine bladder TCC tissue but not in normal bladder epithelium was considered supportive evidence that COX-2 inhibition by piroxicam may play a key role as a therapeutic adjuvant (13). More recently, COX-2 expression was found not to be correlated with response of dogs with TCC to piroxicam therapy. However, reduction in tumor volume after oral piroxicam was strongly associated with induction of apoptosis and reduction in urine basic fibroblast growth factor concentration (14). Although the mechanism of its antitumor effects remains unclear, piroxicam alone induced remission in 17% of dogs with TCC in a previous study (9). Recent reports have documented the chemopreventative and antitumor activity of COX-2 inhibitors against bladder cancer, colorectal cancer, and other carcinomas (15–24). The use of COX inhibitors as part of a treatment protocol for invasive TCC, therefore, warrants additional investigation.

The anthracenedione, mitoxantrone (Novantrone; Immunex Corporation, Seattle, WA), has known antitumor activity against human and canine bladder cancer (25–27). Because the toxicity profile of mitoxantrone does not include nephrotoxicity, one would anticipate that its use in combination protocols with nonsteroidal anti-inflammatory drugs would be less likely to precipitate renal disease than protocols featuring platinum compounds. The purpose of this Veterinary Cooperative Oncology Group study was to evaluate the efficacy of combined therapy using mitoxantrone and piroxicam in a canine model of invasive human TCC.

MATERIALS AND METHODS

Subjects and Eligibility. This study was a multi-institutional Veterinary Cooperative Oncology Group trial based out of the University of Missouri–Columbia Department of Veterinary Medicine and Surgery following guidelines for clinical trial evaluation of client-owned animals as set forth by the University of Missouri–Columbia Animal Care and Use Committee. Subjects for the study were client-owned pet dogs with naturally occurring cancer. Entry requirements for dogs in this study included measurable TCC as diagnosed by cytological or histopathological evaluation of tumor tissue, no previous chemotherapy, no complicating disease, and informed client consent. With the exception of days when dogs were undergoing clinical evaluation or mitoxantrone treatment, the dogs lived at home and were not hospitalized.

Study Design. This was a prospective, multi-institutional veterinary clinical trial evaluating therapy for naturally occurring canine TCC of the bladder. The objective was to determine whether mitoxantrone and piroxicam combination therapy would be well tolerated and induce remission more often than

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

T: primary tumor
Tis Carcinoma *in situ*
T_0 No evidence of tumor
T_1 Superficial papillary tumor
T_2 Tumor invading the bladder wall with induration
T_3 Tumor invading neighboring organs
N: regional node (RLN)
N_0 No evidence of RLN involvement
N_1 RLN involved
N_2 RLN and juxta RLN involved
M: distant metastasis
M_0 No evidence of distant metastasis
M_1 Distant metastasis detected

either agent used alone, based on historical data from previous canine studies.

Baseline evaluations included hematology (complete blood count with differential and platelet count) and serum biochemical analysis, including blood urea nitrogen and creatinine, urinalysis, three-view thoracic radiographs, and tumor measurement via ultrasound. For ultrasound measurement, the bladder was emptied via catheterization, followed by infusion of 1–2 ml/kg of 0.9% NaCl, and measurements were recorded in three dimensions. Tumor volume was recorded in cubic millimeters using the formula, (length $\times$ width $\times$ height) $\times$ $\pi/6$. The amount of saline infused was recorded and used for subsequent bladder infusions during restaging. Clinical tumor stage was determined according to the criteria established by the World Health Organization for canine bladder tumors (Table 1; Ref. 28). Tumor restaging with identical ultrasound measurement techniques, chest radiographs, complete blood counts, urinalyses, and serum biochemical evaluations were performed before the third treatment (on day 42) and every 3 months after protocol completion for at least 1 year. Previous trials assessing chemotherapy for canine TCC have scheduled tumor measurements on days 0 and 42 (10) or days 0, 28 and 56 (9). The evaluation protocol required anesthesia, standardized bladder distension, and measurement using ultrasound. Additional repetitive measurements would have entailed greater risk for patients and potentially compromised protocol compliance.

All dogs received mitoxantrone by i.v. administration at a dosage of 5 mg/m^2 over 5 to 10 min every 21 days for four treatments. Piroxicam was administered p.o. (0.3 mg/kg/day) for the life of the dog or for the duration of study enrollment. Mitoxantrone was discontinued in the event of PD or unacceptable toxicity.

Tumor responses were defined as: CR, complete resolution of all clinical, radiographic, and ultrasonographic evidence of tumor; PR, $\geq$50% decrease in tumor volume with no new tumor lesions; SD, <50% change in tumor volume and no new tumor lesions; and PD, $\geq$50% increase in tumor volume or development of new tumor lesions. In addition, a subjective clinical response score (improved *versus* no improvement) was recorded after two treatments (on day 42), based on the dog owners' assessment of change in clinical signs for which the dog was first presented. End points included subjective clinical improvement after two treatments, measurable response after two treat-

Table 2 Subject characteristics for dogs with TCC of the bladder

Age (yr); ($n = 55$)	
Median	11
Mean	10.6 (range, 5–16.5; SD = 2.1)
Gender ($n = 55$)	
Intact male	2
Castrated male	14
Intact female	0
Spayed female	39
Weight ($n = 55$)	
≤16 kg	39
>16 kg	16
Tumor T stage ($n = 49$)	
T_1	2
T_2	40
T_3	7
Metastasis at presentation ($n = 55$)	
Yes	6
No	49

ments, TTF (time from initiation of therapy until PD or death), and overall survival time (time from initiation of therapy until death). When PD was noted, alternative therapy was offered off study, and dogs were censored in the analysis at that date.

Statistical Analysis. Independent variables examined included patient weight (≤16 kg *versus* >16 kg), age (<10 years *versus* ≥10 years), gender group (male, male castrated, female, female spayed), presence or absence of metastasis at time of first presentation, tumor T stage, number of mitoxantrone treatments (<4 *versus* 4), subjective clinical improvement assessment (yes, no), and measurable clinical response (CR and PR, SD, PD). Initially, means ± SEs and medians ± quartiles were calculated for all dependent and independent variables. Frequencies were calculated for all possible levels of categorical variables. The affect of independent variables on time to treatment failure and survival time were determined using a Kaplan-Meier product limit survival analysis. Dogs that were lost to follow-up were taken off protocol for alternative therapy or died because of causes unrelated to the TCC of the bladder were considered censored in the initial analysis. A second analysis was then performed in which dogs taken off protocol were assigned a death date on the day they were removed. This second analysis was performed to permit comparison with a previous canine study (9) in which censoring was performed in such a manner. Patterns of survival were deemed to differ when the Log Rank P was <0.05. A Fischer's exact test was used to examine the relationship between subjective clinical response (improved or not improved) and measurable tumor response (CR and PR *versus* SD and PD). Associations were considered significant when <0.05.

RESULTS

Fifty-five dogs from 20 institutions were enrolled in the study between May 1998 and February 2000. Six of 55 dogs (11%) had metastatic disease at the time of presentation to the lymph nodes, lungs, or spleen. Subject and tumor characteristics are summarized in Table 2. Thirty-nine dogs received all four doses of mitoxantrone, 1 received three, 7 received two treatments, and 2 dogs received only the first mitoxantrone treat-

ment. Six dogs were excluded from analysis because of incomplete enrollment information or follow-up. Of the 49 dogs with complete enrollment information, 2 had stage T_1 disease, 40 had stage T_2 disease, and 7 had stage T_3 disease.

Complete measured response data were available for 48 dogs. For the 48 dogs with response data analyzed, measurements indicated 1 CR, 16 PR, 22 SD, and 9 PD for an overall measurable response rate (CR and PR) of 35.4%. The 2 dogs that received only one dose of mitoxantrone were classified as having PD but were euthanatized before follow-up tumor measurements were obtained for verification of disease progression. Of dogs for which notation of subjective clinical improvement was available ($n = 48$), 36 (75%) were noted to exhibit clinical improvement, whereas 12 (25%) showed no improvement in clinical signs. Of the 48 dogs with complete enrollment and response data, 18 had no evidence of metastatic disease at death, 15 had confirmed metastatic disease (lung, lymph node, spleen, bone), and 15 were not evaluated for metastatic disease.

The treatment protocol produced GI, hematological, and renal side effects in some dogs. GI side effects occurred in 18% of dogs and included diarrhea and/or hematochezia ($n = 6$), vomiting ($n = 3$), and gastric ulceration ($n = 1$). One dog required hospitalization, fluid therapy, and addition of misoprostol to his protocol but continued with therapy. One dog was dropped from the study after two doses because of owner dissatisfaction regarding GI toxicity. Three dogs required addition of misoprostol to their protocols to combat GI side effects, and piroxicam was discontinued in 2 dogs after their day 42 evaluations. Hematological side effects occurred in 10% of patients. Specifically, 5 dogs developed neutropenia (defined as a segmented neutrophil count < 3000/μl) after the first ($n = 4$) or second dose ($n = 1$) of mitoxantrone. Dose reduction of mitoxantrone by 25% was recommended in 4 of 5 dogs, and all were able to receive a full course (four total doses) of chemotherapy. Azotemia without renal failure occurred in 5 dogs (10%) and was attributed to prerenal causes. Renal failure was documented in 5 dogs (10%) based on azotemia and isosthenuria. Of the dogs developing renal failure, a definitive cause was found in 2 cases. One dog was determined upon necropsy evaluation to have renal amyloidosis. One dog developed renal failure secondary to tumor-related ureteral obstruction. Renal disease in the other 3 dogs was of unknown etiology and was, thus, regarded as a protocol-related toxicity, although 1 was retrospectively noted to have had renal azotemia at the time of study enrollment.

The median time to treatment failure was 194 days (mean = 219 days ± SE = 25; range = 0–460 days), and the median survival time was 350 days (mean = 308 days ± SE = 30; range = 10–675 days). Fourteen of 49 dogs with complete data had metastatic disease at the time of death. Deaths in 28 of 49 dogs were related to their TCC. Factors found to be significantly related to time to treatment failure included number of mitoxantrone treatments completed ($P < 0.0001$), subjective assessment of clinical improvement ($P < 0.0001$), and measurable response ($P < 0.0001$). All other variables examined did not significantly affect time to treatment failure. Subjective clinical improvement was significantly associated with measurable tumor response ($P = 0.002$). Variables that were significantly related to survival time included number of mitoxantrone
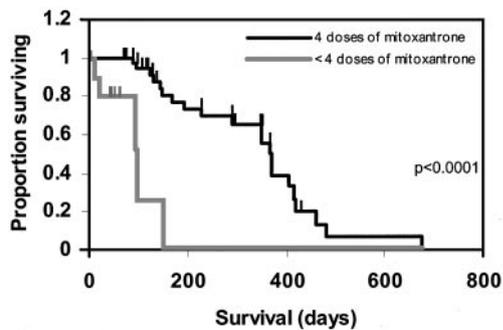
Fig. 1 Product limit survival curves for dogs with TCC receiving 4 or <4 doses of mitoxantrone. *Tick marks* on survival curves indicate censored dogs.
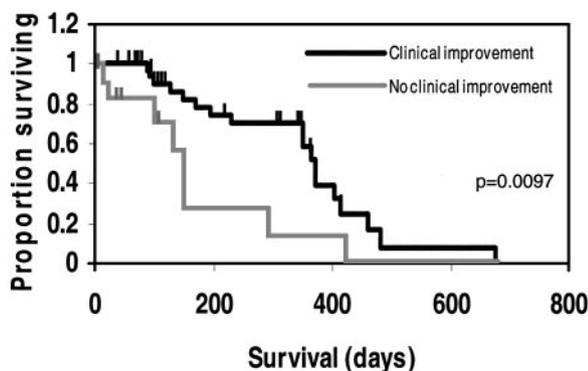

Fig. 2 Product limit survival curves for dogs with TCC experiencing subjective clinical improvement or no clinical improvement with mitoxantrone and piroxicam therapy. *Tick marks* on survival curves indicate censored dogs.

Fig. 3 Product limit survival curves for dogs with TCC experiencing PD, SD, or CR or PR with mitoxantrone and piroxicam therapy. *Tick marks* on survival curves indicate censored dogs.

treatments completed ($P < 0.0001$; Fig. 1), subjective assessment of clinical improvement ($P = 0.0097$; Fig. 2), and measurable response ($P = 0.0040$; Fig. 3). No other variables examined significantly affected survival time.

DISCUSSION

The patient characteristics for this study were similar to previous reports of canine TCC of the bladder (5, 9, 10, 29, 30). The disease most commonly occurs in older female dogs, as was the case in this study where the median age was 11 years (mean = 10.6, SD = 2.1) and females comprised 71% of the initial study population. Metastatic disease was confirmed at the time of diagnosis in 6 dogs (11%), somewhat less than in previous reports where metastatic rates ranged from 14 to 37% (5, 31, 32). Although documentation of tumor stage at time of death was complete for only 33 dogs, the metastatic rate was at least 31%. Again, this is in keeping with reported metastatic rates for this tumor in dogs.

The purpose of this prospective clinical trial was to evaluate combination therapy using mitoxantrone and piroxicam for treatment of canine TCC of the bladder. The protocol induced measurable response in 35% of dogs for a median response duration of 194 days and median survival time of 350 days. When analyzed by an alternative method where dogs were
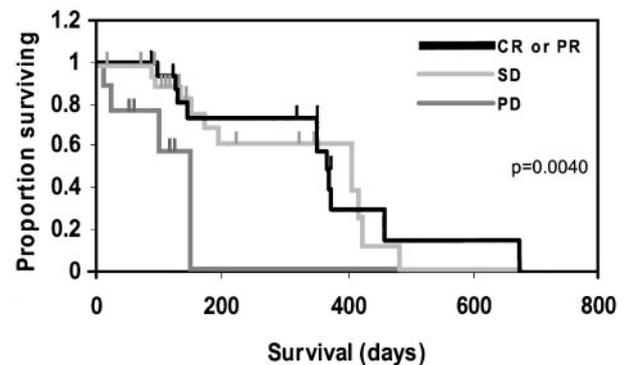
assigned death dates rather than censored on the day they were taken off protocol to pursue other therapy, the median time to treatment failure was 160 days, and the median survival time was 291 days. This compares favorably with results obtained in a similarly analyzed group of dogs treated with piroxicam alone, which had a remission rate of 17% and median survival time of 181 days (9). Although a randomized clinical trial comparing piroxicam alone to piroxicam and mitoxantrone combination therapy would be needed to establish the significance of this difference, the fact that the response rate doubled and median survival time improved by 60% with this combination protocol over the previous report of piroxicam alone suggests that the protocol reported here may provide a clinical advantage.

Drug-related toxicity noted with this protocol included GI irritation in 18% of dogs, neutropenia in 10%, and renal failure unattributable to other causes in 6% of dogs with complete follow-up. This overall incidence of GI and renal toxicity was identical to that reported with piroxicam alone for treatment of dogs with TCC of the bladder (9). GI irritation was attributed primarily to the effects of piroxicam and was, in all but 1 case, managed with addition of misoprostol to the protocol. Neutropenia was a dose-limiting toxicity in 4 dogs that required dose reductions by 25%, although sepsis was not a sequela of therapy reported for any dogs. Renal failure was documented in 3 dogs and was attributed to drug toxicity in the absence of other known etiology. A previous protocol combining piroxicam and cisplatin for the treatment of canine TCC resulted in renal failure in 12 of 14 dogs, underscoring the increased risk of nephrotoxicity when nonsteroidal anti-inflammatory agents are combined with some chemotherapeutic agents (10). Dogs with TCC are at risk for obstructive urinary disease that may induce renal failure as well. Although the incidence of renal failure was low and no different from that reported for piroxicam monotherapy, patients must be carefully screened to ensure adequate renal function before considering this protocol and should be monitored throughout the course of treatment.

The factors affecting TTF included total number of mitoxantrone treatments received and whether dogs experienced clinical and measurable tumor responses. These variables were likely interrelated, in that dogs with PD were assigned a TTF of 0 days and were less likely to remain on study and receive all

four doses of mitoxantrone than responders. Likewise, the same variables significantly affected overall survival. The availability of euthanasia for veterinary patients must be taken into account when evaluating survival data. Dogs are often euthanatized when they experience PD or a decline in perceived quality of life. As a result, the patients in veterinary oncology trials often are euthanatized rather than living out the natural course of their disease, thus decreasing overall survival times reported. Of interest is the fact that dogs in this study that were perceived by their owners to have improvement in clinical signs had longer survival times than those without subjective improvement, even when they did not have measurable reduction in tumor size. One explanation is that owners may have been less likely to resort to euthanasia for dogs with apparent clinical improvement and good quality of life. Another possibility is that resolution of clinical signs such as hematuria and dysuria may positively impact survival by improving nutritional intake and slowing progression of anemia, even when measurable tumor response is not achieved.

Perhaps a more important end point reported here is overall survival time. Although response rates provide one measure of comparison between protocols, responses that are not durable or that do not positively affect survival are of limited clinical relevance. This issue was recently addressed in a manuscript that reported results of a Southwest Oncology Group trial evaluating paclitaxel and carboplatin for treatment of advanced TCC (33). In the Southwest Oncology Group trial, response rates were poor (overall response proportion = 20.7%), but overall survival differed little from that in two other studies (34, 35) with much higher response proportions (50 and 65%). Although we cannot directly compare our results to those obtained with piroxicam alone without performing a randomized study, both response proportion and overall survival were higher than previously reported with piroxicam. Therefore, additional evaluation of this protocol for treatment of advanced TCC in veterinary and human patients is warranted.

ACKNOWLEDGMENTS

REFERENCES

1. Greenlee, R. T., Hill-Harmon, M. B., Murray, T., and Thun, M. Cancer statistics, 2001. CA - Cancer J. Clin., 51: 15–36, 2001.

2. Patton, S. E., Hall, M. C., and Ozen, H. Bladder cancer. Curr. Opin. Oncol., 14: 265–272, 2002.

3. Meluch, A. A., Greco, A., Burris, H. A., O'Rourke. T., Ortega, G., Steis, R. G., Morissey, L. H., Johnson, V., and Hainsworth, J. D. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a Phase II trial of the Minnie Pearl Cancer Res. Network. J. Clin. Oncol., 19: 3018–3024, 2001.

4. Lehmann, J., Retz, M., and Stockle, M. Chemotherapy in the post-MVAC era: the case for adjuvant chemotherapy. World J. Urol., 20: 144–150, 2002.

5. Knapp, D. W., Glickman, N. W., DeNicola, D. B., Bonney, P. L., Lin, T. L., and Glickman, L. T. Naturally-occurring canine transitional cell carcinoma of the urinary bladder. A relevant model of human invasive bladder cancer. Urol. Oncol., 5: 47–59, 2000.

6. Moore, A. S., Cardona, A., Shapiro, W., and Madewell, B. R. Cisplatin (cisdiaminedichloroplatinum) for treatment of transitional cell carcinoma of the urinary bladder or urethra. A retrospective study of 15 dogs. J. Vet. Intern. Med., 4: 148–152, 1990.

7. Chun, R., Knapp, D. W., Widmer, W. R., DeNicola, D. B., Glickman, N. W., Kuczek, T., Degortari, A., and Han, C. M. Phase II clinical trial of carboplatin in canine transitional cell carcinoma of the urinary bladder. J. Vet. Intern. Med., 11: 279–283, 1997.

8. Chun, R., Knapp, D. W., Widmer, W. R., Glickman, N. W., DeNicola. D. B., and Bonney, P. L. Cisplatin treatment of transitional cell carcinoma of the urinary bladder in dogs: 18 cases (1983–1993). J. Am. Vet. Med. Assoc., 209: 1588–1591, 1996.

9. Knapp, D. W., Richardson, R. C., Chan, T. C. K., Bottoms, G. D., Widmer, W. R., DeNicola, D. B., Teclaw, R., Bonney, P. L., and Kuczek, T. Piroxicam therapy in 34 dogs with transitional cell carcinoma of the urinary bladder. J. Vet. Intern. Med., 8: 273–278, 1994.

10. Knapp, D. W., Glickman, N. W., Widmer, W. R., DeNicola, D. B., Adams, L. G., Kuczek, T., Bonney, P. L., DeGortari, A. E., Han, C., and Glickman, L. T. Cisplatin versus cisplatin combined with piroxicam in a canine model of human invasive urinary bladder cancer. Cancer Chemother. Pharmacol., 46: 221–226, 2000.

11. Knapp, D. W. Tumors of the urinary system. In: S. J. Withrow and E. G. MacEwen (eds.), Small Animal Clinical Oncology, Ed. 3, pp. 490–499, Philadelphia: W. B. Saunders, 2001.

12. Helfand, S. C., Hamilton, T. A., Hungerford, L. L., Jeglum, K. A., and Goldschmidt, M. A. Comparison of three treatments for transitional cell carcinoma of the bladder in the dog. J. Am. Anim. Hosp. Assoc., 30: 270–275, 1994.

13. Khan, K. N., Knapp, D. W., DeNicola, D. B., and Harris, R. K. Expression of cyclooxygenase-2 in transitional cell carcinoma of the urinary bladder in dogs. Am. J. Vet. Res., 61: 478–481, 2000.

14. Mohammed, S. I., Bennett, P. F., Craig, B. A., Glickman, N. W., Mutsaers, A. J., Snyder, P. W., Widmer, W. R., DeGortari, A. E., Bonney, P. L., and Knapp, D. W. Effects of the cyclooxygenase inhibitor, piroxicam, on tumor response, apoptosis, and angiogenesis in a canine model of human invasive urinary bladder cancer. Cancer Res., 62: 356–358, 2002.

15. Castelao, J. E., Yuan, J. M., Gago-Domingues, M., Yu, M. C., and Ross, R. K. Non-steroidal anti-inflammatory drugs and bladder cancer prevention. Br. J. Cancer, 82: 1364–1369, 2000.

16. Dempke, W., Rie, C., Grothey, A., and Schmoll, H. J. Cyclooxygenase-2: a novel target for cancer chemotherapy? J. Cancer Res. Clin. Oncol., 127: 411–417, 2001.

17. Farrow, D. C., Vaughan, T. L., Hansten, P. D., Stanford, J. L., Risch, H. A., Gammon, M. D., Chow, W. H., Dubrow, R., Ahsan, H., Mayne, S. T., Schoenberg, J. B., West, A. B., Rotterdam, H., Fraumeni, J. F., Jr., and Blot, W. J. Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. Cancer Epidemiol. Biomarker. Prev., 7: 97–102, 1998.

18. Gupta, R. A., and DuBois, R. N. Colorectal cancer prevention and treatment by inhibition of cyclooxygenase-2. Nat. Rev. Cancer, 1: 11–21, 2001.

19. Hida, T., Kozaki, K., Muramatsu, H., Masuda, A., Shimizu, S., Mitsudomi, T., Sugiura, T., Ogawa, M., and Takahashi, T. Cyclooxygenase-2 inhibitor induces apoptosis and enhances cytotoxicity of various anticancer agents in non-small cell lung cancer cell lines. Clin. Cancer Res., 6: 2006–2011, 2000.

20. Nishimura, G., Yanoma, S., Mizuno, H., Kawakami, K., and Tsukuda, M. A selective cyclooxygenase-2 inhibitor suppresses tumor growth in nude mouse xenografted with head and neck squamous carcinoma cells. Jpn. J. Cancer Res., 90: 1152–1162, 1999.

21. Norrish, A. E., Jackson, R. T., and McRae, C. U. Nonsteroidal anti-inflammatory drugs and prostate cancer progression. Int. J. Cancer, 77: 511–515, 1998.

22. Rao, K. V. N., Detrisac, C. J., Steele, V. E., Hawk, E. T., Kelloff, G. J., and McCormick, D. L. Differential activity of aspirin, ketoprofen, and sulindac as cancer chemopreventative agents in the mouse urinary bladder. Carcinogenesis (Lond.), *17:* 1435–1438, 1996.

23. Smalley, W., and DuBois, R. N. Colorectal cancer and nonsteroidal anti-inflammatory drugs. Adv. Pharmacol., *39:* 1–20, 1997.

24. Thun, M. J., Namboodiri, M. M., and Heath, C. W., Jr. Aspirin use and reduced risk of fatal colon cancer. N. Engl. J. Med., *325:* 1593–1596, 1991.

25. Ogilvie, G. K., Obradovich, J. E., Elmslie, R. E., Vail, D. M., Moore, A. S., Straw, R. C., Dickinson, K., Cooper, M. F., and Withrow, S. J. Efficacy of mitoxantrone against various neoplasms in dogs. J. Am. Vet. Med. Assoc., *198:* 1618–1621, 1991.

26. Rocha, T. A., Mauldin, G. N., Patnaik, A. K., and Bergman, P. J. Prognostic factors in dogs with urinary bladder carcinoma. J. Vet. Int. Med., *14:* 486–490, 2000.

27. Yaman, L. S., Yudakul, T., Zissis, N. P., Arikan, N., and Yasar, B. Intravesicular mitoxantrone for superficial bladder tumors. Anti-Cancer Drugs, *5:* 95–98, 1994.

28. Owen, L. N. TNM classification of tumors in domestic animals, Ed. 1, p 34.Geneva: World Health Organization, 1980.

29. Hayes, H. M. Canine bladder cancer: epidemiologic features. Am. J. Epidemiol., *104:* 673–677, 1976.

30. Priester, W. A., and McKay, F. W. The occurrence of tumors in domestic animals. NCI Monogr. 54, 1980.

31. Burnie, A. G., and Weaver, A. D. Urinary bladder neoplasia in the dog; a review of seventy cases. J. Small Anim. Pract., *24:* 129–143, 1983.

32. Norris, A. M., Laing, E. J., Valli, V. E. O., Withrow, S. J., Macy, D. W., Ogilvie, G. K., Tomlinson, J., McCaw, D., Pidgeon, G., and Jacobs, R. M. Canine bladder and urethral tumors: a retrospective study of 115 cases (1980–1985). J. Vet. Intern. Med., *6:* 145–153, 1992.

33. Small, E. J., Lew, K., Redman, B. G., Petrylak, D. P., Hammond, N., Gross, H. M., Eastham, J. A., and Crawford, E. D. Southwest Oncology Group study of paclitaxel and carboplatin for advanced transitional-cell carcinoma: the importance of survival as a clinical trial end point. J. Clin. Oncol., *18:* 2537–2544, 2000.

34. Vaughn, D. J., Malkowicz, S. B., Zoltick, B., Mick, R., Ramchandani, P., Holroyde, C., Armstead, B., Fox, K., and Wein, A. Paclitaxel plus carboplatin in advanced carcinoma of the urothelium: an active and tolerable outpatient regimen. J. Clin. Oncol., *16:* 255–260, 1998.

35. Redman, B. G., Smith, D. C., Flaherty, L., Du, W., and Hussain, M. Phase II trial of paclitaxel and carboplatin in the treatment of advanced urothelial carcinoma. J. Clin. Oncol., *16:* 1844–1848, 1998.

Clinical Evaluation of Mitoxantrone and Piroxicam in a Canine Model of Human Invasive Urinary Bladder Carcinoma

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