

Evaluation of Mitoxantrone with Piroxicam as First Line Therapy for Carcinomas of the Prostate in Dogs

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ABSTRACT

Carcinomas of the prostate in dogs are a heterogeneous group of aggressive cancers that collectively carry a poor prognosis. The aim of this retrospective study was to evaluate the efficacy of using mitoxantrone along with piroxicam for the treatment of carcinomas of the prostate. Survival time, time to treatment failure, subjective and objective responses, prognostic indicators, and toxicity were evaluated. Twenty-five dogs were included in this study. Metastatic disease was diagnosed in 56% of dogs and 72% at the time of death. Seventy-four percent of dogs had a subjective improvement in clinical signs with the majority of dogs responding within 30 days. No objective responses were noted. Median time to treatment failure was 105 days. Median survival time for all dogs was 155 days. Toxicity was minimal with GI toxicity being most common.

Results suggest that adding mitoxantrone to piroxicam therapy does not appear to be beneficial in the treatment of carcinomas of the prostate in dogs.

INTRODUCTION

Prostate carcinomas are a group of rare neoplasms in dogs, representing less than 1% of all diagnosed canine cancers.¹ These spontaneous cancers can be used as a model for human prostatic carcinoma.² In dogs, most prostatic carcinomas are suspected to be ductal or urothelial in origin, rather than acinar as in humans.³⁻⁵ Ductal tumors display similar biologic behavior in both people and dogs, as they are prone to early metastasis.⁶ The absence of androgen receptors found in ductal epithelial cells suggests that canine prostatic carcinoma formation is likely androgen independent. Controversy still exists regarding the effects of castration on the development of canine prostatic carcinoma. However, three studies revealed that castrated dogs were at an increased risk

for developing prostatic carcinoma, with odds ratios ranging from 3.86-4.34.^{3,5-6}

Metastatic, hormone-refractory, androgen independent prostate cancer in people is similar in biologic behavior to canine prostatic carcinoma. In men, 85-90% of those diagnosed with this form of prostate cancer have bone scan evidence of metastasis at some point in the disease process.⁷ Evidence of soft tissue metastatic disease is noted in 20-40% of these patients, with pelvic lymph nodes being the most common site.⁷ In dogs, the rate of metastasis at the time of death is approximately 80%, with the most common sites being the lungs, regional lymph nodes, liver, and bone.⁸ Skeletal metastasis were documented in 22% of dogs, with the majority of these lesions found in the axial skeleton.⁸

There is little published on the efficacy of treatment for prostate tumors in dogs. Androgen ablation is unlikely to be a useful therapy in dogs, as the tumors arise mostly from an androgen independent region. Radical prostatectomy is recommended in men with clinically localized disease who have a life expectancy of at least 10 years.⁷ Prostatectomy has been evaluated in dogs and leads to significant and persistent urinary incontinence.⁹ In men, with clinically localized disease, external beam radiation therapy or brachytherapy are valid treatment options.⁷ External beam radiation therapy was not found to be useful in one small case series of dogs using palliative intraoperative radiation therapy.¹⁰

Due to the highly metastatic nature of this disease in dogs, local treatment alone is unlikely to be effective. Cyclooxygenase (Cox) inhibitors are reported to be successful in treating various types of urogenital carcinomas, alone or in conjunction with chemotherapy in dogs.¹¹⁻¹⁴ Cox-2 inhibitors have antitumor activity in a variety of epithelial tumors and Cox-2 receptors are frequently overexpressed in human prostatic tumors.¹⁵ Two studies indicated that approximately 75-88% of canine prostate carcinomas also express Cox-2.^{11,16} A recent study

showed that Cox inhibitors were effective in the treatment of canine prostatic carcinoma, dogs that received a Cox inhibitor had a median survival time (MST) of 6.9 months while dogs that did not had a MST of only 0.7 months.¹¹

To the authors' knowledge, there are no published reports on the efficacy of chemotherapy, alone or in conjunction with a Cox inhibitor, for the treatment of carcinomas of the prostate in dogs. Mitoxantrone has palliative clinical benefit for men with androgen resistant prostate carcinoma.¹⁷ Combined with piroxicam, mitoxantrone improved response rates and increased survival times for invasive urinary bladder tumors in dogs when compared to piroxicam alone.¹²

Piroxicam is a non-selective Cox inhibitor and the exact mechanism of antitumor activity is unclear at this time.¹² Reducing prostaglandin synthesis, thus increasing apoptosis, inhibiting neoplastic cell proliferation, and restoring normal immune response have all been postulated as possible mechanisms.¹⁵

Mitoxantrone, an anthracenedione, works through topoisomerase II mediated DNA breakage, binding to nucleic acids which inhibits DNA and RNA synthesis, and inducing apoptosis.¹⁸ Advanced urogenital tumors can result in azotemia, therefore, using an agent that spares renal function is preferable.¹⁹ Mitoxantrone has not been associated with nephrotoxicity and, therefore, would be a suitable chemotherapy to use along with piroxicam for this disease.

The purpose of the study was to evaluate the efficacy of mitoxantrone in addition to piroxicam for the treatment of carcinoma of the prostate in dogs. Survival time, time to treatment failure, subjective and objective responses, prognostic indicators, and toxicity were evaluated. As there is limited information regarding treatment for carcinomas of the prostate, this paper can assist in providing additional information to the practicing clinician.

MATERIAL AND METHODS

Medical records from December 2005 through January 2011 at The Veterinary Cancer Center (formerly Veterinary Oncology and Hematology Center), Brightheart Veterinary Referral and Emergency Center (formally known as Center for Specialized Veterinary Care), and New England Veterinary Oncology Group were reviewed. We identified 25 dogs with carcinomas of the prostate that were treated with mitoxantrone and piroxicam. Patients were included if:

- they had a histologic or cytologic diagnosis of carcinoma of the prostate
- evidence of measurable disease at diagnosis
- did not receive any previous chemotherapy, did not have evidence of any

other major systemic disease, and had adequate staging prior to initiating therapy.

Information regarding patient signalment, clinical signs, and physical examinations were collected from medical records. Staging tests included:

- complete blood count (CBC)
- serum biochemistry profile
- chest radiographs (CXR)
- abdominal ultrasound (AUS)

Regional metastasis was defined as the cytologic or histologic presence of carcinoma cells in regional lymph nodes or from evidence noted via imaging studies. Distant metastasis was defined as the presence of a mass effect in any organ beyond the regional lymph nodes, with or without cytologic confirmation. Any missing or incomplete

Table 1. VCOG-Common Terminology Criteria For Adverse Events

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Vomiting	<3 episodes in 24 hours	3-5 episodes in 24hrs; <3 episodes/day for >2 days but <5 days; Parenteral (IV or SC) indicated <24hrs	>5 episodes in 24hrs; vomiting>4 days; IV fluids or PPN/TPN indicated >24hrs	Life-threatening (e.g., hemodynamic collapse)	Death
Diarrhea	Increase of >2 stools per day over baseline	Increase of 2-6 stools per day over baseline; Parental (IV or SC) fluids indicated <24hrs; not interfering with ADL	Increase of >6 stools per day over baseline; incontinence; IV fluids>24hrs; hospitalization; interfering with ADL	Life threatening (e.g., hemodynamic collapse)	Death
Anorexia	Coaxing or dietary change required to maintain appetite	Oral intake altered (<3d) without significant weight loss; oral nutritional supplements indicated	Of 3-5 day duration; Associated with significant weight loss or malnutrition; IV fluids, tube feeding or TPN indicated. Abdominal pain, fever, change in bowel habits, ileus, peritoneal signs	Life threatening consequences	Death
Neutropenia	1,500/ μ L - <LLN	1,000-1,499/ μ L	500-999/ μ L	<500/ μ L	-
Anemia	30% - <LLN	25 - 30%	20 – 25%	<20%	-
Creatinine	>ULN-1.5 X ULN	>1.5-2.0 X ULN	>2.0-3 X ULN	>3 X ULN	Death
	Mild	Moderate	Severe	Life-threatening	Death

Hrs=hours

ADL=activities of daily living (eating, sleeping, defecating, and urinating)

ULN=upper limit of normal

LLN=lower limit of normal

information was obtained from phone calls made to the local referring veterinarian or the owners.

Records were also reviewed for information regarding response and tolerability to therapy by way of evaluating the history given by owners, CBC, serum biochemistries, CXR, and AUS. These tests were not performed at standard intervals for each patient. Two different types of responses were evaluated. Subjective response was defined as improvement or resolution of stranguria, dysuria, pollakiuria and/or hematuria, or improvement or resolution of tenesmus. Objective response was evaluated through interpretation of CXR and AUS. Antitumor objective responses were assessed according to the World Health Organization (WHO) tumor criteria guidelines. A complete response (CR) was defined as 100% resolution of radiographic/ultrasonographic evidence of disease; a partial response (PR) was defined as $\geq 50\%$ reduction in measurable disease, but not CR, stable disease (SD) did not meet criteria for PR or progressive disease, and progressive disease (PD) was defined as $\geq 25\%$ increase in one or more tumors or ap-

pearance of new lesions noted.²⁰

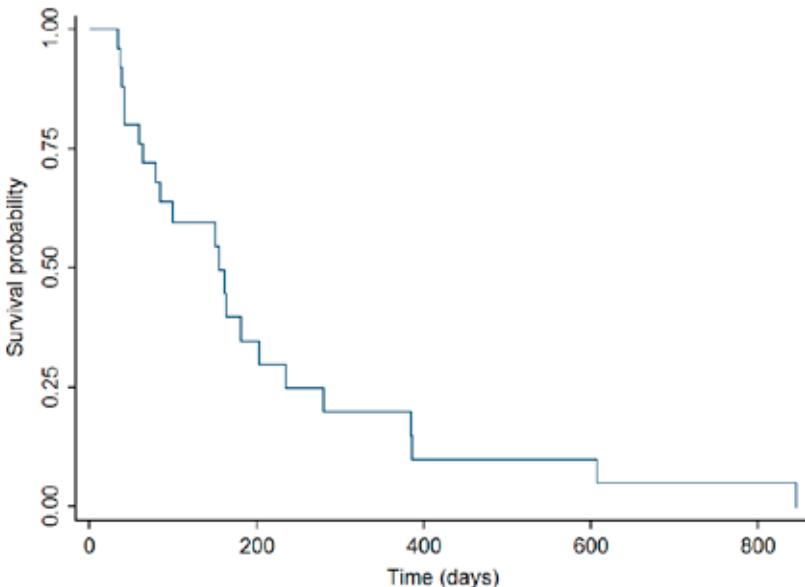
All dogs received mitoxantrone by intravenous administration every 3 weeks at a starting dose of 5-5.5mg/m². Exact starting dose was dependent on clinician discretion. All dogs were concurrently receiving piroxicam given orally at 0.3mg/kg once daily. Dogs were continued on piroxicam until death or renal toxicity occurred.

Medical records were reviewed for any toxicities. Gastrointestinal (GI) events were defined as any evidence of anorexia, vomiting, or diarrhea. Hematologic toxicity was determined through evaluation of a CBC, which was performed before every chemotherapy treatment. A biochemistry profile was intermittently performed based upon overseeing clinicians' discretion. Gastrointestinal, hematologic, and biochemical toxicity were graded based on the Veterinary Comparative Oncology Group (VCOG-CTCAE) scheme 21 (see table 1).

The variables evaluated for influence on overall survival time included:

- the presence of clinical signs at diagnosis

Figure 1. Kaplan–Meier curve depicting the survival time of all dogs (25 dogs) that were treated with mitoxantrone and piroxicam



- subjective improvement
- the presence of metastasis at diagnosis.

Statistical differences were considered significant if $P < 0.05$.

Objective time to progression (oTTP) was defined as the time from initial therapy until objective progressive disease was documented, or death occurred. Subjective time to progression (sTTP) was defined as the time from initial therapy until clinical progression or death. Time to treatment failure was defined as the time of initiation of treatment to rescue therapy or treatment failure. Overall survival time (OST) was defined as the time from initiation of therapy until death. When progressive disease was noted, many dogs received rescue therapy. The rescue drug of choice was dependent on the preference of the clinician, and dogs were censored from the time to progression analyses at that date. Dogs that were lost to follow-up, received rescue therapy, or died of an unrelated cause were considered censored at the time of their last examination, the date they received rescue therapy, or the date of death, respectively. Therefore, there were two different time intervals analyzed: time to treatment failure and survival time.

The Kaplan-Meier method of survival function estimation was used to describe time to progression of disease and survival; results are presented as median times to respective outcome and 95% confidence intervals. Potential determinants to outcomes were evaluated using proportional hazards regression; results are presented as hazard ratios and 95% confidence intervals. P-values < 0.05 were considered statistically significant.

RESULTS

Twenty-five dogs with confirmed carcinoma of the prostate were included in this study. Breeds represented included 5 mixed-breed dogs, 3 Labrador retrievers, 2 Golden retrievers, 2 Miniature schnauzers, 2 Shetland sheepdogs, 2 Standard poodles, and 1 each of the following breeds: Pit bull terrier, Border collie, Wheaton terrier, Basset hound,

Boxer, German shepherd dog, Weimaraner, Australian shepherd, and Tibetan terrier. The median weight of dogs was 24.2 kilograms (range of 7.7-62.1 kilograms), and median age was 10.5 years (range of 7-13 years). All dogs were castrated. A diagnosis of carcinoma was made via cytology in 18 dogs and histology in seven dogs.

At diagnosis 14/25 (56%) dogs had evidence or suspicion for metastatic disease. Thirteen (52%) dogs had regional metastasis, and 2/25 (8%) had distant metastasis. One of these dogs had evidence of both regional and distant metastasis. Five of 13 (38%) dogs with regional metastatic disease were confirmed by cytologic evaluation. One of 2 dogs with distant metastatic disease was confirmed through cytology. At the time of death, 18/25 (72%) total dogs had confirmed or suspected metastatic disease. The most common locations for metastatic development included:

- regional lymph nodes (n=3)
- abdominal masses not associated with any particular organ (n=3)
- lungs (n=2)
- lumbar vertebra (n=1)
- intestines (n=1)
- bi-cavitary effusion (n=1).

One dog developed seizures after significant progressive disease, and it was suspected that the dog developed metastasis to the central nervous system, although this was never confirmed.

All dogs received mitoxantrone chemotherapy once every three weeks for at least one treatment. The median number of mitoxantrone doses was 4 (range 1-11 doses). The median dose of mitoxantrone was 5.3 mg/m², (range, 5-6mg/m²). All dogs received piroxicam therapy at 0.3mg/kg once daily. Ten dogs underwent rescue therapy(s) after progressive disease occurred. Rescue therapies were variable in type and number and based upon attending doctor preference and included:

- carboplatin (n=4)
- carboplatin/ gemcitabine (n=3)

- adriamycin (n=2)
- urethral stenting (n=2)
- gemcitabine (n=1)
- navelbine (n=1)
- cisplatin (n=1)
- cyberknife radiation therapy (n=1)

Complete subjective response data was available for interpretation in 19 dogs. There were five dogs that did not present with lower urinary signs or tenesmus, and therefore, were unable to be included in the interpretation data. Initial clinical signs were unavailable in one dog. Fourteen of the 19 (74%) dogs had a subjective response, meaning owners perceived an improvement in their dogs' urination and/or defecation. Ninety-three percent of these dogs responded within one month of the first treatment.

Complete objective response data was available for 21 dogs and there were 11 SD and 10 PD. None of the patients experienced a CR or PR. One dog received only one dose of mitoxantrone, and is still alive at the time of the writing of this manuscript, but no further diagnostics have been done. Three dogs did not have any follow up diagnostic after their initial staging.

Prognostic factors that were associated with survival time included the presence of initial clinical signs (both urinary signs and tenesmus) and the presence of regional metastatic disease. Survival for dogs without urinary signs (164 days) was longer ($P=0.048$) than dogs with urinary signs (151 days). Dogs that presented with tenesmus had a MST of 64 days compared to a MST of 203 days for dogs that did not have tenesmus ($P=0.012$). There was a significant ($P=0.006$) difference in survival time for dogs with (85 days) and without (235 days) metastatic disease at the time of diagnosis.

The MST for all dogs was 155 days (95% confidence interval (CI), 79 to 203 days, see figure 1). The median time to treatment failure was 105 days (95% CI, 46 to 193 days). sTTP for all dogs was 85 days (95% CI, 56-182 days). The oTTP for all dogs was 81 days (95% CI, 46-170). Two

dogs had urethral stents placed as a rescue therapy, one of which also received cyberknife radiation therapy and survived for 100 days. The other dog had a survival time of 60 days. Twenty-two dogs died of tumor related causes, one dog died of unrelated cause (congestive heart failure), one dog was lost to follow-up, and one dog is still alive at the time when the manuscript was written. These three dogs were censored during analysis.

In general, mitoxantrone and piroxicam were well tolerated. Gastrointestinal toxicity information was available in 20 dogs and was the most common adverse event noted in this study. Of the 20 dogs evaluated, 8 (40%) had evidence of GI toxicity characterized as grade 1 (n=5), grade 2 (n=1), and grade 3 (n=2). The GI toxicity included anorexia (n=8), vomiting (n=4), and diarrhea (n=2). All gastrointestinal signs resolved with supportive care, and no dogs required hospitalization. Hematologic toxicity information was available in 23 dogs, and occurred in 26% of patients evaluated. Specifically, neutropenia (n=2 grade 1 and n=1 grade 3). The dog that experienced severe neutropenia required hospitalization. Both of the mild cases occurred after the 2nd treatment of mitoxantrone and the severe neutropenia occurred after the 1st dose. Anemia (grade 1) occurred in three dogs and did not require any treatment. Serum creatinine levels were elevated in seven dogs while receiving mitoxantrone with piroxicam. Of these seven dogs, it was characterized as grade 1 (n=5), grade 3 (n=1) and grade 4 (n=1).

DISCUSSION

The purpose of this study was to evaluate the antitumor activity of mitoxantrone and piroxicam in dogs for the treatment of carcinomas of the prostate. We chose this protocol because it is an effective combination therapy for other urogenital carcinomas in dogs.¹² We evaluated survival time, time to treatment failure, subjective and objective responses, prognostic indicators, and toxicity. No objective responses were noted, and

11 dogs had SD while 9 had PD. Seventy-four percent of dogs that were evaluated had a subjective clinical improvement. Despite a significant number of dogs that experienced a subjective response, the time to treatment failure was limited, 105 days.

The patient population in this study was similar to previous studies evaluating canine prostatic tumors.¹¹ In this study, regional metastasis were confirmed or suspected at diagnosis in 14/25 of dogs, which is slightly higher than a recent study.¹¹ In that same study 7/35 dogs had suspected distant metastasis (two had pulmonary and five had skeletal). The current study, however, indicated a lower number of dogs suspected to have distant metastasis at diagnosis (2/25) with one dog having pulmonary and one dog having skeletal involvement. At the time of death, 72% had evidence of metastatic disease, similar to a previous report.⁸ The survival time in this study was shorter when compared to a recent study that evaluated the use of a single agent Cox inhibitor for canine prostate tumors.¹¹ However, both studies revealed a statistically significant difference in survival time when metastatic disease was present at the time of diagnosis. Possible explanations for the difference in survival time between these two studies may be a difference in the population of dogs.

Although all dogs had similar staging initially, subsequent staging during treatment was not uniformly conducted. Most dogs were diagnosed with metastatic disease based on ultrasonographer interpretation. The use of different ultrasonographers may result in variable measurements, as documented in a recent publication evaluating bladder TCC, which may lead to over or under-estimation of certain variables in this study.²² Although the tumor locations were different, the principles leading to measurement discrepancy still apply. This is a subjective determination, as noted in people there is a lack of consensus in regards to the size of a normal vs metastatic pelvic lymph node.²³ Necropsies were not performed, therefore, we were unable to confirm the

presence of metastatic disease in those cases.

This protocol was tolerated well, with mild GI toxicity being the most common adverse effect. The number of dogs that developed GI toxicity was similar to previous reports.¹² Both mitoxantrone and piroxicam can cause GI toxicity.²⁴⁻²⁵ Three dogs developed neutropenia, one of which was severe (grade 3). The hematologic data needs to be evaluated cautiously because CBC results were extracted from the records at the time of each chemotherapy visit, not at the expected nadir for mitoxantrone (7-10 days post chemotherapy).¹⁸ This could, therefore, result in underestimation of the number of hematologic adverse events. Elevated serum creatinine levels occurred in seven dogs (all but one of these dogs had no evidence of renal disease prior to starting therapy). The majority of the azotemia was grade 1, with one dog having grade 3 toxicity and another having grade 4 toxicity. The grade 4 toxicity was suspected to be caused by progressive disease, as a large trigonal mass was found on AUS resulting in secondary hydroureter and hydronephrosis. The causes of the azotemia in the other cases include obstructive disease secondary to tumor extension into the urethra or bladder or nephrotoxicity secondary to the Cox inhibitors.^{19,26} Cox inhibitors can induce renal failure by inhibiting prostaglandin production in the afferent and efferent arterioles, leading to a reduction in renal blood flow.²⁶

The prognostic factors affecting survival time included the presence of initial clinical signs (both urinary signs and tenesmus) and the presence of regional metastasis at the time of diagnosis. Dogs presenting without clinical signs likely had a better quality of life, potentially resulting in the owners' willingness to continue with therapy until clinical signs developed. Similarly, in human medicine, stage and performance score are some of the most important clinical prognostic indicators for prostatic carcinoma.⁷ In general, men with extensive disease that are clinically affected fare worse than others.⁷

The results of this study showed that

many dogs succumb to both local, as well as, distant disease progression. Therefore, using a combination of local therapy along with systemic therapy may be warranted. Future studies using other chemotherapeutic agents such as docetaxel may be reasonable therapeutic options.⁷ In men with androgen-independent prostate cancer, docetaxel is the only agent that has been shown to prolong survival.⁷ Intra-arterial chemotherapy which allows direct access of cytotoxic agents to the tumor may also be beneficial.²⁷

It is possible that even though mitoxantrone and a Cox inhibitor is a successful treatment option for canine bladder TCC¹² this combination may not be effective for other urogenital tumors. A potential theory proposes that the biologic behavior of carcinoma of the prostate may be more aggressive or more chemoresistant than carcinomas of the bladder, resulting in a higher metastatic rate and subsequently shorter survival times. Also, because of the close proximity of the prostate to the urethra, only minimal progressive disease is required to result in clinical signs which can subsequently effect survival time.

As with all retrospective studies, there are limitations to this study. One limitation is the small number of dogs with a histopathologic diagnosis. Although cytologic diagnosis is not as accurate, a previous publication revealed an 80% correlation between prostatic cytology and histopathology.²⁸ Even with histopathology, it can be difficult to differentiate urothelial from ductal carcinoma, despite the use of immunohistochemical stains.²⁹ In suspected prostatic tumor cases, the large majority of clinicians obtain a diagnosis of carcinoma of the prostate through cytology as it is minimally invasive, safe, and cost effective. This is analogous to diagnosing dogs with lymphosarcoma, as most clinicians achieve a diagnosis and treatment plan based solely from cytology, despite the many subtypes that exist. Therefore, a paper like this can provide clinically relevant information on carcinomas of the prostate. As with most retrospective studies,

there was incomplete information regarding staging, toxicity and follow up. In addition, treatment was not randomized, an inherent weakness of retrospective studies that highlights the potential issue of having multiple institutions involved in a study. Some of the variables assessed were subjective in nature, specifically, owners' assessment of their pet's clinical response to therapy.

The combination of mitoxantrone and piroxicam induced a subjective response rate of 74%. However, no objective responses were observed. Furthermore, the time to tumor progression as well as MST was short. This protocol does not appear to improve upon historical treatment options for canine carcinomas of the prostate.¹¹ A randomized clinical trial would need to be performed to accurately compare the use of a piroxicam alone to piroxicam and mitoxantrone. Further studies are needed to define a more effective protocol for this disease.

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