Evaluation of piroxicam for the treatment of oral squamous cell carcinoma in dogs

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Objective—To evaluate the use of piroxicam for the treatment of oral squamous cell carcinoma in dogs.

Design—Prospective case series.

Animals—17 dogs with measurable oral squamous cell carcinoma.

Procedure—Dogs were treated with piroxicam at a dosage of 0.3 mg/kg (0.14 mg/lb) of body weight, PO, every 24 hours until progressive disease or unacceptable signs of toxicity developed or the dog died.

Results—One dog had a complete remission (maxillary tumor), and 2 dogs had partial remissions (lingual tumor and tonsillar tumor). An additional 5 dogs had stable disease, including 1 with a maxillary tumor, 2 with mandibular tumors, and 2 with tonsillar tumors. Variables associated with tumor response were not identified. Median and mean times to failure for the 3 dogs that had a remission were 180 and 223 days, respectively. Median and mean times to failure for the 5 dogs with stable disease were 102 and 223 days, respectively. Time to failure was positively associated with tumor response and negatively associated with tumor size. One dog had mild adverse gastrointestinal tract effects that resolved with the addition of misoprostol to the treatment regimen.

Conclusions and Clinical Relevance—Results suggest that piroxicam may be useful in the treatment of dogs with oral squamous cell carcinoma; response rate was similar to that reported for other cytotoxic treatments. Larger-scale studies are warranted to determine what role piroxicam may have, alone or in combination with other treatments, for the treatment of dogs with oral squamous cell carcinoma. (J Am Vet Med Assoc 2001;218:1783–1786)

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oral cancers account for approximately 7% of all cancers in dogs, and 20 to 30% of all oral cancers in dogs are squamous cell carcinomas (SCC).1 Oral SCC typically affects older dogs, with mean age at the time of diagnosis being 10 years.1 Prognostic factors reported for dogs with localized oral SCC include location of the tumor in the oral cavity, tumor size, and success of the first treatment attempt.1,3 Rostrally located SCC of the mandible and maxilla are usually locally aggressive but have a low metastatic potential. Therefore, radical surgery, radiation therapy, or a combination of surgery and radiation therapy is considered the most appropriate form of treatment, with a generally good prognosis for long-term survival in these dogs.1,10 Although lingual SCC has been reported to have a moderate rate of metastasis, dogs with small low-grade resectable lingual tumors may still benefit from partial glossectomy.1,13 Local control of tonsillar SCC is usually achieved with surgical resection or radiation therapy; however, SCC at this site are highly metastatic, and most dogs will succumb to metastatic disease within 1 year after the diagnosis is made.1,13-14 Therefore, surgical resection and radiation therapy are the mainstays of treatment in dogs with localized oral SCC; however, metastatic disease is still a major cause of death in dogs with lingual and tonsillar SCC.

The role of chemotherapy in the treatment of dogs with nonresectable or metastatic oral SCC, either alone or in combination with surgery or radiation therapy, has not been critically evaluated. In humans, head and neck SCC are considered chemoresistant, resulting in high morbidity and mortality rates in patients with advanced disease.3,27 Bleomycin, cisplatin, mitomycin-C, and doxorubicin reportedly have only limited antitumor effects in dogs and cats with SCC of all sites,28 and responses observed in dogs with oral SCC were reported to be poor and of short duration. Clearly, a more effective treatment for nonresectable or metastatic SCC in dogs is needed.

Piroxicam, a nonsteroidal anti-inflammatory drug (NSAID), has been shown to have antitumor effects in dogs and humans.22-24 In a previous study,24 for instance, 2 of 4 dogs with oral SCC had a remission following treatment with piroxicam. Additionally, piroxicam was well tolerated and relatively inexpensive, compared with more traditional cytotoxic treatments. The purpose of the study reported here was to evaluate the response to piroxicam in dogs with oral SCC. It was hoped that results of the present study could be used to determine whether larger-scale studies are justified.

Materials and Methods

The study protocol was approved by the Purdue Animal Care and Use Committee. Dogs with histologically confirmed measurable oral SCC were eligible for inclusion in the study; owners of all dogs included in the study provided informed consent. Tumor staging was performed at the Purdue University Veterinary Teaching Hospital and included physical examination, tumor measurements, thoracic radiography, radiography or, when indicated, computed tomography of the oral cavity, CBC, serum biochemical analyses, and urinalysis. Tumor staging was scheduled to be performed prior to and 1 and 2 months after initiation of piroxicam treatment and at 3-month intervals thereafter or more frequently if clinically indicated.

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Following initial tumor staging, dogs were treated with piroxicam at a dosage of 0.3 mg/kg (0.14 mg/lb) of body weight, PO, every 24 hours. If anorexia, vomiting, or melena occurred, administration of piroxicam was discontinued until clinical signs resolved. Treatment with piroxicam was then reinstituted, and misoprostol (3 to 5 μg/kg [1.4 to 2.3 μg/lb], PO, q 8 h) was added to the treatment regimen. Treatment with piroxicam was continued until progressive disease or unacceptable signs of toxicity developed or the dog died.

Tumor response was classified as complete remission (CR; complete resolution of all clinical, radiographic, and cytologic evidence of tumor), partial remission (PR; > 50 but < 100% decrease in tumor volume without development of any new tumor lesions), stable disease (SD; ≤ 50% change in tumor volume and no new tumor lesions at 30 days), or progressive disease (PD; > 50% increase in tumor volume or development of new tumor lesions). Time to failure was defined as the time from the start of piroxicam treatment until PD or death.

Tumors were staged according to the World Health Organization TNM system for classification of tumors in domestic animals.5 Tumor size (T status) was defined as T1 (maximum tumor diameter ≤ 2 cm), T2 (maximum tumor diameter 2 to 4 cm), or T3 (maximum tumor diameter > 4 cm); T status was further subclassified as a (no evidence of bone invasion) or b (evidence of bone invasion). Lymph node status (N status) was defined as N0 (no evidence of regional lymph node involvement), N1 (enlarged movable ipsilateral regional lymph nodes), N2 (enlarged movable contralateral or bilateral regional lymph nodes), or N3 (regional lymph nodes fixed); N status was further subclassified as a (regional lymph nodes considered not to contain tumor growth) or b (regional lymph nodes considered to contain tumor growth). Regional lymph nodes that were clinically normal in size and not accessible for biopsy were considered not to contain tumor growth. Regional lymph nodes that were enlarged and not biopsied were considered to contain tumor growth. Distant metastasis status (M status) was defined as M0 (no evidence of distant metastasis) or M1 (evidence of distant metastasis).

Statistical analyses—Two-tailed Fisher exact tests were used to test for associations between tumor location, TNM stage, previous treatment, and tumor response to piroxicam. Associations between tumor location, TNM stage, tumor response, and prior treatment with time to failure were analyzed using a Wilcoxon test. For all analysis, values of P < 0.05 were considered significant.

Results

Patient and tumor characteristics—Seventeen dogs were enrolled in the study. Median and mean ages of dogs at the time of enrollment in the study were 10 and 10.1 years, respectively (range, 5 to 15 years). Median and mean weights of the dogs were 20 and 23 kg, respectively (44 and 31 lb; range, 7 to 46 kg [15 to 101 lb]). There were 13 spayed females, 2 castrated males, and 2 sexually intact males. Six dogs were of mixed breeding; the remaining 11 dogs consisted of 2 Miniature Poodles, 2 German Shepherd Dogs, and 1 of each of the following breeds: Bouvier des Flandres, Doberman Pinscher, English Springer Spaniel, Chow Chow, Gordon Setter, American Eskimo, and Old English Sheepdog. Four dogs had maxillary tumors (T2aN0M0, T2aN0M0, T2aN0M0, T2aN0M0), 5 had mandibular tumors (T1bN1bM0, T1bN1bM0, T1bN1bM0, T1bN1bM0, T1bN1bM0), 3 had lingual tumors (T1aN0M0, T1aN0M0, T1aN0M0), 1 had a mandibular tumor with evidence of metastasis to the regional lymph nodes (T1aT1bN1bM0), and 2 had mandibular tumors (T1aN0M0, T1aN0M0, T1aN0M0, T1aN0M0, T1aN0M0, T1aN0M0, T1aN0M0, T1aN0M0, T1aN0M0, T1aN0M0, T1aN0M0, T1aN0M0). The regional lymph nodes were biopsied in 5 of the 6 dogs with regional lymph node enlargement; 3 dogs had evidence of metastasis to the regional lymph nodes, and the other 2 did not. The enlarged regional lymph nodes in the 1 dog that did not undergo lymph node biopsy were considered to contain tumor growth for purposes of this study. The remaining 11 dogs had clinically normal regional lymph nodes. Lymph nodes in the other 7 dogs were not accessible for biopsy and were considered to be free from tumor growth for purposes of this study.

One dog with a tonsillar tumor (T2aN0M0) received 2 doses of cisplatin (60 mg/m2 of body surface area, IV, 3 weeks apart) prior to inclusion in the present study. Treatment with piroxicam was initiated 3 weeks after the second dose of cisplatin was given because of PD despite cisplatin treatment. One dog with a lingual tumor (T1aN0M0) underwent local excision of the mass 8 months prior to inclusion in the present study; the size of the lingual tumor prior to surgery was not known.

Response to treatment—One dog had a CR, and 2 dogs had a PR; therefore, overall remission rate was 18%. The dog with a CR had a maxillary tumor (T1bN0M0) and had not received any previous treatment. One dog with a PR had a lingual tumor with metastasis to the regional lymph nodes (T1aN0M0) that progressed after surgery prior to inclusion in the present study; the dog had PD 2 weeks after the initiation of piroxicam treatment but had a PR 48 days after initiation of piroxicam treatment. The other dog with a PR had a tonsillar tumor without evidence of metastasis to the regional lymph nodes (T1aN0M0) and had not received any previous treatment. None of the dogs with mandibular tumors had a remission.

Five (29%) dogs had SD, including 1 with a maxillary tumor (T1bN0M0), 2 with mandibular tumors (T1bN1bM0 and T1bN1bM0), and 2 with tonsillar tumors (T1bN1bM0 and T1aN1bM0). None of the dogs with lingual tumors had SD. Response to piroxicam treatment was not significantly associated with tumor location, TNM stage, or previous treatment.

Median and mean times to failure for the 3 dogs with CR and PR were 180 and 223 days, respectively (123, 180, and 365 days). Median and mean times to failure for the 5 dogs with SD were 102 and 246 days, respectively (123, 180, and 365 days). Time to failure was positively associated with tumor response (P < 0.001) and negatively associated with T status (P < 0.039).

Piroxicam was well tolerated. Only 1 dog had adverse gastrointestinal tract effects; signs were mild and did not recur when piroxicam was administered in conjunction with misoprostol. Two dogs continued to receive piroxicam after PD was detected because owners perceived improvement in their dogs’ quality of life.

Discussion

Results of the present study suggest that piroxicam may be useful for the treatment of dogs with oral SCC, in that 3 (18%) had a remission, and another 5 (29%)
had SD. Although these rates may seem low, they compare favorably to responses seen with other cytotoxic therapies. For example, in 10 unpublished canine cases with oral SCC identified in the Veterinary Medical Data Base at Purdue University that were treated with cisplatin alone, only 1 (10%) obtained remission, and only 1 (10%) had SD.

The age, breeds, and weight of the dogs included in the present study, as well as tumor locations, were similar to those previously reported for dogs with oral SCC. A sex predisposition has not been reported; thus, there is no obvious explanation for the lower number of males, compared with females in the present study.

The size and metastatic rate of maxillary and mandibular tumors included in this study appeared to be greater than that reported in the literature. This is most likely attributable to the fact that dogs with smaller localized mandibular and maxillary tumors were more likely to have been treated by surgical excision and, therefore, were not included in the study.

Important limitations of the present study include the low number of cases, the lack of a comparison treatment group, and variations in determining lymph node status. Even with these limitations, however, we believe the response rates justify additional studies of the use of piroxicam in the treatment of dogs with SCC. In addition, although tumor location was not associated with tumor response, response rates in dogs with tonsillar (of 5 dogs with tonsillar tumors, 1 had a PR, and 2 had SD) and lingual (of 3 dogs with lingual tumors, 1 had a PR) tumors warrant further evaluation with larger numbers of cases, because these tumors can be metastatic and difficult to control with traditional cytotoxic treatments.

An interesting finding was the dog with a lingual tumor and cervical lymph node metastasis that had PD during a follow-up examination 15 days after initiation of piroxicam treatment. When the dog was next examined 48 days after initiation of piroxicam treatment, PR was evident. This suggests that the tumor response to piroxicam may be delayed in dogs, as in humans with metastatic renal carcinoma treated with interferon. Further study of this potential effect is needed. In addition, although resection of the lingual tumor in this dog may have contributed to the prolonged survival time, the purpose of the present study was to evaluate tumor response and time to failure, not survival time.

The dog treated with cisplatin prior to inclusion in this study had PD while receiving piroxicam. The effect, if any, of previous cisplatin treatment on response to piroxicam is not known; however, in the present study, previous treatment was not associated with tumor response or time to failure.

Piroxicam and other NSAID inhibit prostaglandin synthesis through a reduction in prostaglandin E2 production, inhibition of angiogenesis, interaction with growth factors, and induction of apoptosis. In addition to their antitumor effects, NSAID may improve the quality of life of affected dogs through their anti-inflammatory and analgesic effects. Although the intent of this study was not to measure the quality of life of dogs receiving piroxicam, 3 owners did make unsolicited comments regarding the decrease in signs of pain and increased activity in their pets, regardless of tumor response. Future studies should incorporate a questionnaire regarding the owners’ perceived quality of life of their pets.

Toxic effects of piroxicam and other NSAID are most likely attributable to their effects on cyclooxygenase. Various animal and human cancers overexpress cyclooxygenase-2. Cyclooxygenase-1, on the other hand, is important in protecting the gastric mucosa and preserving renal blood flow. Piroxicam and many other NSAID inhibit both cyclooxygenase-1 and cyclooxygenase-2, and inhibition of cyclooxygenase-1 is most likely responsible for the toxic renal and gastrointestinal effects associated with these drugs. In the present study, only 1 dog developed toxic effects, and these effects resolved with the addition of misoprostol to the treatment regimen.


