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REVIEW ARTICLE

COX-2 Inhibitors for Cancer Treatment in Dogs

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ABSTRACT

Cancer is one of the main causes of death in canines and felines, and this fact is probably related to the increase in the longevity of these species. The longer the animals live, the higher the exposure to carcinogenic agents will be. With the high incidence of cancer in companion animals, new studies are currently being performed with the aim of finding therapeutic options which make the complete inhibition of the development of neoplasms in animals possible in the future. The correlation of cyclooxygenase-2 (COX-2) whith the development of cancer opens the way for the use of new therapeutic approaches. This relationship has been suggested based on various studies which established an association between the chronic use of nonsteroidal anti-inflammatory drugs (NSAID) and a decrease in the incidence of colon carcinoma. As cancer progresses, COX-2 participates in the arachidonic acid metabolism by synthesizing prostaglandins which can mediate various mechanisms related to cancer development such as: increase in angiogenesis, inhibition of apoptosis, suppression of the immune response, acquisition of greater invasion capacity and metastasis. Accordingly, overexpression of this enzyme in tumors has been associated with the most aggressive, poor-prognosis cancer types, especially carcinomas. Therefore, treatments which use COX-2 inhibitors such as coxibs, whether administered as single agents or in combination with conventional antineoplastic chemotherapy, are an alternative for extending the survival of our cancer patients.

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INTRODUCTION

Cancer is one of the main causes of death in canines and felines, and this fact is probably related to the increase in the longevity of these species. Prevention of contagious infectious diseases by vaccination schemes and technological advances which yield greater diagnostic & therapeutic precision, in addition to provision of specific diets through balanced and therapeutic foods, allow dogs and cats to have a longer life. Therefore, the higher incidence of neoplasms is a consequence of the longer exposure to carcinogenic agents (Rodaski and Piekars, 2009).

With the high incidence of cancer in companion animals, new studies are currently being performed with the aim of discovering therapeutic options which make the complete inhibition of the development of neoplasms in animals possible in the future. The correlation of cyclooxygenase-2 (COX-2) with cancer development provides a new therapeutic modality against this disease. This relationship has been postulated with basis on various studies which established an association between chronic use of nonsteroidal anti-inflammatory (NSAID) drugs and decreased incidence of colon carcinoma in the mid-90s (Thun *et al*., 1993).

Physiopathology of the cyclooxygenases

The products of the arachidonic acid metabolism comprise a set of mediators which modulate the inflammatory responses. These metabolites result from oxidation of arachidonic acid caused by the action of the

enzyme phospholipase A2 on cell membrane phospholipids (Wang *et al*., 2006; Souza *et al*., 2009). Oxidation of arachidonic acid can occur through the lipooxigenase or the cyclooxygenase enzymatic pathways (Queiroga *et al*., 2005).

Cyclooxygenase acts on membrane phospholipids by converting arachidonic acid into a stable prostaglandin endoperoxide, PGG2. PGG2 is reduced to prostaglandin H2 (PGH2), which is then available to serve as substrate for the synthesis of other prostaglandins such as PGE2, PGD2 and PGF2α. PGH2 can also be converted into a prostacyclin (PGI2) or a thromboxane (TXA2) (Queiroga *et al*., 2005).

There are at least two types of cyclooxygenases which exert distinct physiologic functions in the organism: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) (Spugnini *et al*., 2005; Wang *et al*., 2006; Souza *et al*., 2009; Queiroga *et al*., 2010). A third type, cyclooxygenase-3 (COX-3), has also been described as a COX-1 variant and it is more abundant in the cerebral cortex and in the heart (Wolfesberger *et al*., 2006).

COX-1 is constitutively expressed in many tissues and is responsible for the synthesis of the prostaglandins which regulate normal cellular function. When inhibited, COX-1 causes side effects such as gastric ulcers and renal toxicity (Murray and Brater, 1993; Davies, 1995).

COX-2 is usually absent in normal cells (Davies, 1995; Pires *et al*., 2010); however, its expression can be induced by growth factors, inflammatory reactions, tumoral promoters and various oncogenes (Spugnini *et al*., 2005; Pires *et al*., 2010; Queiroga *et al*., 2010).

During cancer development, this enzyme participates in the arachidonic acid metabolism by synthesizing prostaglandins which can mediate various processes such as increase in cell proliferation and angiogenesis, suppression of the immune system and reduction of the apoptosis rate (Lavalle *et al*., 2009).

There are two main NSAIDs groups: non-specific COX-1 and COX-2 inhibitors and specific COX-2 inhibitors. The latter exclusively bind COX-2, which results in fewer gastrointestinal side effects (Queiroga *et al*., 2010).

Experimental studies in rats confirmed that the use of selective COX-2 inhibitor drugs exert a protective effect against tumor development in the gastrointestinal system (Oshima *et al*., 1996; Kawamori *et al*., 1998), which verifies the importance of COX-2 in the carcinogenic process (Eberhat *et al*., 1994; Subbaramaiah *et al*., 1996; Hida *et al*., 1998). Other studies found evidence of reduction in tumor growth and in metastasis development, which suggests an emerging role of selective COX-2 inhibitors in the prevention and treatment of cancer (Denkert *et al*., 2003; Howe, 2007).

Association of COX-2 expression with neoplasias

With basis on experimental studies, mechanisms associated with tumoral promotion such as increase in angiogenesis, inhibition of apoptosis, modulation of immune response, and greater invasive and metastatic capacities have been proposed to explain the consequences of COX-2 overexpression (Cao and Prescott, 2002; Millanta *et al*., 2006; Howe, 2007).

This enzyme is associated with the production of vascular endothelial growth factor (VEGF), which stimulates the growth of endothelial cells and, thereby, promotes angiogenesis, which is indispensable for most solid tumors as newly formed blood vessels provide nutrients and warrant their growth and survival. In addition, angiogenesis is crucial for the development of metastases (Knottenbelt *et al*., 2006).

Prostaglandin E2 (PGE2) is known to be the main COX-2 product involved in tumor development and progression (Mohammed *et al*., 2001). Colony-stimulating factors secreted by tumor cells activate monocytes and macrophages and stimulate these cells to synthesize PGE2, which inhibits lymphokine regulation, T cells, B cell proliferation and the cytotoxic activity of natural killer (NK) cells. PGE2, in turn, inhibits the production of tumor necrosis factor (TNF) and induces the production of interleukin-10 (IL-10), which contributes to suppression of the immune response (Dannenberg *et al*., 2001; Wang *et al*., 2006).

Accordingly, overexpression of COX-2 in tumors has been associated with a poor prognosis and with the most aggressive cancers, especially carcinomas (Lascelles, 2007). Studies in Veterinary Medicine have shown an increase in the expression of COX-2 and PGE2 in various canine tumors (León-Artozqui and Morcate, 2008) (Table 1), such as intestinal (McEntee *et al*., 2002), pancreatic (Mohammed *et al*., 2004), ovarian (Borzacchiello *et al*., 2007), prostatic (L'Eplattenier *et al*., 2007), mammary gland (Doré *et al*., 2003; De Nardi *et al*., 2007; Queiroga *et al*., 2007; Dias Pereira *et al*., 2009; De Nardi *et al*., 2009; Lavalle *et al*., 2009; Queiroga *et al*., 2010), nasal cavity (Mullins *et al*., 2004; Heller *et al*., 2005; Impellizeri and Esplin, 2008) and oral (Pires *et al*., 2010) neoplasms.

Increased expression of COX-2 in patients with mammary neoplasms is associated with lesser survival in bitches (Queiroga *et al*., 2005; Lavalle *et al*., 2009; Queiroga *et al*., 2010). In addition, De Nardi *et al*. (2007) and Dias Pereira *et al*. (2009) found that COX-2 was overexpressed in the majority of the metastatic lesions studied as well as in primary mammary neoplasms, which contributes to the suspicion that this enzyme possesses angiogenic and invasive properties in the mestastatic process.

COX-2 is also found in precancerous cutaneous lesions such as actinic keratosis. In humans, irradiation with ultraviolet light B (UVB) induces overexpression of this enzyme in keratinocytes, which suggests its involvement in skin cancer development after prolonged exposure to sunlight (Bakhle, 2001).

Studies suggest that cyclooxygenase-2 inhibits apoptosis by inducing expression of the proto-oncogene Bcl and that this anti-apoptotic effect can extend the survival of abnormal cells, which provides more time for the accumulation of genetic mutations that result in neoplastic transformations (Surh *et al*., 2001; Bol *et al*., 2002; Cao and Prescott, 2002). One study has found evidence of reduction of Bcl-2 expression and induction of apoptosis in cancer cells after the use of COX-2 inhibitors (Cao and Prescott, 2002).

Table 1: Intensity of expression of COX-2 in various canine's tumors

Tumor Type	Intensity of Expression of COX-2 (%)
Tumors That Express COX-2	
Oral SCC	65-100
Skin SCC	100
Oral Melanoma	60
Prostatic Carcinoma	56-75
TCC of the Bladder	58-100
Mammary Tumor	62–100*
Colorectal Carcinoma	65
Nasal Carcinoma	73-87
Renal Cell Carcinoma	67
Osteosarcoma	23-79
Tumors that Do Not Express COX-2	
Lymphoma	0
Histiocytic Sarcoma	0
Hemangiosarcoma	0

SCC: squamous cell carcinoma, TCC: transitional cell carcinoma. Source: León-Artozqui and Morcate (2008). *Depends on the Histological Type (Mohammed *et al.*, 2004; Queiroga *et al.*, 2005; Millanta *et al.*, 2006; Queiroga *et al.*, 2007; Lavalle *et al.*, 2009).

With the catalytic activity of COX-2, DNA damage by free radicals is potentiated and results in permanent lesions in the genomic DNA, which provides support for the hypothesis that inflammatory processes lead to the onset of cancer (Zha *et al*., 2001; Dong *et al*., 2003).

These studies verify the important role of COX-2 in the pathogenesis of cancer and suggest that programmed inhibition of this enzyme through the use of selective COX-2 inhibitors, selective COX-2 inhibitors may be effective for chemoprevention and treatment of cancer.

Use of COX-2 inhibitors for the treatment of cancer

Drugs which inhibit COX-2 have shown to possess potential effects on the reduction of cancer incidence and the ability to potentiate the effects of antineoplastic chemotherapy (Dvory-Sobol and Arber, 2007; Arber, 2008). These drugs are indicated for the treatment of cancer as they exert both preventive and therapeutic effects in spontaneous and experimental canine neoplasia models (Borzacchiello *et al*., 2007; Rossmeisl *et al*., 2009).

The majority of NSAIDs inhibit both COX-1 and COX-2; whereas, coxibs, which constitute a new generation of NSAIDs, are selective COX-2 inhibitors (Jones and Budsberg, 2000).

Coxibs developed for use in Veterinary Medicine are currently being intensely studied for the treatment of neoplasias in dogs (León-Artozqui and Morcate, 2008). Owing to their high selectivity for COX-2, these molecules are believed to exhibit a more potent antitumoral effect than traditional NSAIDs; in addition, the safety provided by coxibs is much higher as judged by the lower extent of their associated side effects.

The most studied COX-2 inhibitors are carprofen, deracoxib, firocoxib, meloxicam and piroxicam, which are all administered orally (Lascelles, 2007). Carprofen is used at a dose of 2mg/kg every 12 hours or 4mg/kg every 24 hours and is considered to be a preferential COX-2 inhibitor. Deracoxib is administered at a dose of 1 to 2 mg/kg every 24 hours and is considered to be a specific COX-2 inhibitor. Firocoxib is used at a dose of 5 mg/kg every 24 hours and is also characterized as a specific inhibitor for this enzyme; whereas, meloxicam is a preferential COX-2 inhibitor prescribed at a dose of 0.2 mg/kg on the first day of treatment and, subsequently, at 0.1 mg/kg every 24 hours. Piroxicam is used at a dose of 0.3 mg/kg every 24 hours or 0.5 mg/kg every 48 hours and is regarded as a non-specific COX inhibitor (Lascelles, 2007).

Piroxicam has demonstrated anticancer effects on some tumors such as transitional cell carcinoma of the bladder and oral squamous cell carcinoma (Lascelles, 2007), and also has produced good results in the treatment of dogs with rectal polyps (Knottenbelt *et al*., 2000). Souza *et al*. (2009) observed a clinical response in all dogs affected by inflammatory mammary carcinoma which were treated with this drug.

Dogs with transitional cell carcinoma treated with piroxicam exhibited the same rate of response to the treatment and survival as those treated with traditional antineoplastic chemotherapy (Knapp *et al*., 1992; Knapp *et al*., 1994). Piroxicam can also be used in combination with conventional antineoplastic chemotherapy as an adjuvant. In cases of transitional cell carcinoma, this medication can be associated with cisplatin and thereby increase the tumoral reduction rate in some cases, even though renal toxicity is frequent and dose-limiting (Mohammed *et al*., 2003).

It is suggested that piroxicam does not induce apoptotic effects on cancer cells; instead, its antineoplastic effecs can be associated with COX-2 inhibition and, consequently, with a decrease in cell proliferation and inhibition of angiogenesis or with an increase in the immune response at the tumor site (Knapp *et al*., 1992; Mutsaers *et al*., 2005; Spugnini *et al*., 2005; Chun and Thamm, 2007; Souza *et al*., 2009).

Meloxicam has been studied by Wolfesberger *et al*. (2006) in dogs with osteosarcoma. These researchers observed inhibition of neoplastic cell growth 48 and 72 hours after treatment with meloxicam at doses of 200, 400 and 600 µM delivered through the intramuscular route, doses which were higher than those recommended for conventional treatment.

Firocoxib has been studied by León-Artozqui and Morcate (2008), who observed an improvement in quality of life in patients with transitional cell carcinoma of the bladder after treatment with firocoxib alone or combined with antineoplastic chemotherapic drugs such as cisplatin; in addition, a significant increase in patient survival was also found.

However, even though the evidence available thus far indicates that various neoplasms exhibit increased COX-2 expression, the effect of treatment with inhibitors of this enzyme on these neoplasms requires further evaluation (Borzacchiello *et al*., 2007; L'Eplattenier *et al*., 2007; Lavalle *et al*., 2009).

Conclusions

Selective cyclooxygenase-2 inhibitors are an alternative for the treatment of neoplasias in dogs and can be used alone or combined with other basic therapies such as antineoplastic chemotherapy. Further studies are required to precisely determine the best doses and the

most effective administration schedules for the treatment of neoplasias in companion animals.

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