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THE ROLE OF COX-2 INHIBITORS IN CANCER TREATMENT

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The non-steroid anti-inflammatory drugs (NSAIDs) are those non-glucocorticoid drugs that suppress inflammation through inhibition of arachidonic acid (AA) metabolism. Intracellular AA is a substrate for cyclooxygenases and lipooxygenases that produce the eicosanoid end products involved in inflammation. Cyclooxygenases add oxygen to AA which creates unstable prostaglandin endoperoxides that are eventually converted to prostaglandins and thromboxanes.

There are two important cyclooxygenases, cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2). COX-1 is responsible for the generation of prostaglandins in many tissues, including the gastrointestinal tract, kidney, and platelets and endothelial cells. These prostaglandins are important regulators of homeostasis and protect the GI tract, regulate hemostasis, and allow the kidney to respond to hypotension. COX-2 produces “inducible” prostaglandins that are needed intermittently by the body in the presence of inflammation. The toxicity and safety profiles of the NSAIDs can be predicted based on the ratio, or selectivity, of COX-1 vs. COX-2 inhibition. However, in vitro studies of selectivity may not be applicable to clinical patients, and the concentrations achieved in vivo may remove selectivity.

One use of COX-2 inhibitors is for pain relief. Cancer patients, especially those with bony involvement, may have chronic pain that is partially responsive to NSAID therapy. However, NSAID therapy alone is unlikely to provide complete analgesia. However, they are synergistic with the opioid analgesics and may allow adequate pain relief with lower opioid drug doses, which minimizes the sedative effects associated with opioid use in dogs and cats.

The NSAID doses required in these combination protocols for pain management may also be lower, which can minimize the risk for adverse GI and renal effects associated with some NSAIDs.

Because COX-2 is upregulated in many types of tumors, the COX-2 inhibitors have drawn a lot of attention for their potential as a cancer management tool. Canine tumors with demonstrated COX-2 expression include nasal epithelial tumors, mammary tumors, colorectal tumors, oral squamous cell carcinoma, renal cell carcinoma, prostatic carcinoma, oral melanoma, osteosarcoma, and transitional cell carcinoma of the urinary bladder. Indeed the NSAID piroxicam has been well studied in bladder cancer and produces similar clinical response rates and survival times as cisplatin chemotherapy in dogs with transitional cell carcinoma of the urinary bladder. Although the mechanisms are not entirely know, inhibiting COX-2 in these patients can result in tumor cell apoptosis and may also affect immune effector cell function and disrupt angiogenesis. Interestingly, cancer therapy, such as photodynamic therapy can increase COX-2 expression in tumors, and the efficacy of chemotherapy and radiation therapy is improved with the addition of COX-2 inhibitors for certain cancers. This suggests and expanding role for COX-2 inhibitors in the management of cancer. However, well controlled randomized clinical trials are necessary to determine the role of COX-2 inhibitors for managing veterinary cancer patients. Epidemiological studies will also be necessary to determine if COX-2 inhibitor use in veterinary medicine has any protective effect against the development of cancer as demonstrated in people on a low dose aspirin protocol.

SUGGESTED READING