The Role of Glucocorticoids and NSAIDs in Cancer Treatment for Dogs and Cats

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GLUCOCORTICOIDs IN CANCER

Scientific Basis
Natural and synthetic glucocorticoids (GCs) exert their functions within the body through the cytoplasmic glucocorticoid receptor, present on most cells.1,2 Following binding, the GC–receptor complex translocates to the nucleus of the cell, where binding to specific GC response elements or other transcription factors can activate or repress gene transcription.1-2 Synthetic GCs (including prednisone/prednisolone and dexamethasone) have been shown to cause apoptosis of malignant lymphocytes,1,3 and thus are tenets of treatment for both human and veterinary hematopoietic tumors, including leukemias, lymphomas, and multiple myeloma.1,3-7

Is Prednisone or Dexamethasone Better?
In adult humans with acute lymphoblastic leukemia, the relative efficacy of prednisone or dexamethasone has been found to be dose dependent. Although dexamethasone may confer a moderately superior outcome, it causes significantly more side effects, leaving the decision of which GC to use up to the attending clinician based on individual patient needs.8 However, this literature is mixed, with other clinical trials showing no advantage of one GC over another.9 In the veterinary literature, it is unclear if prednisone or dexamethasone is superior for the treatment of cancer, or if the GC elected affects remission rates or outcomes. Thus, the decision to use prednisone or dexamethasone is typically at the discretion of the clinician or veterinarian, although most chemotherapy protocols use oral prednisone/prednisolone.

TREATMENT OPTIONS
Glucocorticoids and nonsteroidal anti-inflammatory drugs can be potent primary or adjuvant treatments for a variety of cancers in veterinary medicine.
The doses of GCs used in veterinary cancer chemotherapy protocols are typically those considered to be anti-inflammatory (0.5 to 1 mg/kg/day or 30 to 40 mg/m²/day) rather than immunosuppressive (2 to 3 mg/kg/day or 50 to 60 mg/m²/day for dogs >25 kg), with the exception of very small patients (<10 kg), in which the anti-inflammatory doses mentioned here are immunosuppressive. If given in conjunction with chemotherapy, GCs are also usually tapered quickly to avoid inducing adverse effects.

Use in Treating Specific Cancers

**Lymphoma/Leukemia**

Standard therapy for canine and feline large cell lymphoblastic leukemia and lymphoma is CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone), with some nuance based on location and specific type of malignancy. When standard treatment is declined, GCs alone are often prescribed. A common misconception is that GCs provide palliative care only. However, as previously mentioned, GCs cause apoptosis and death of malignant lymphoid cells, leading to decreased tumor burden and increased quality of life. However, this effect is transient and overall remission time is often short.

A recent study examined the use of GCs alone in the treatment of naïve peripheral nodal B-cell and T-cell canine lymphoma and found that the overall survival time was 50 days (95% confidence interval [CI], 41 to 59 days). Median survival time was significantly longer for dogs with substage a disease (not clinically ill) than for those with substage b disease (clinically ill), and for those with a higher quality of life score at diagnosis as assessed by the owner. Interestingly, dogs with T-cell disease had a longer survival time (90 days; 95% CI, 67 to 109 days) than those with B-cell disease (39 days; 95% CI, 28 to 49 days). This is contrary to the typical finding of dogs with B-cell disease having a better outcome. While this discrepancy could have been due to lack of statistical power, the authors postulated that perhaps dogs with T-cell lymphoma are more sensitive to the effects of GCs, as it appears GCs cause a greater suppression of the blastogenic response of T cells than of B cells.

A similar study in cats has not been completed. However, an overall response rate of 70% of cats to prednisolone alone with extranodal lymphoma has been reported, with only 30% of cats achieving a complete remission. Median survival has been reported to be 60 days, compared with 138 days for cats receiving a variety of chemotherapy protocols. Thus, although dogs and cats both initially respond to GCs, the response is transient.

In addition, eliminating prednisone from the CHOP chemotherapy protocol has not been shown to affect the complete remission rate, median progression-free survival, or overall survival time. Although lack of prednisone was associated with an increased hazard for lymphoma progression and an increased hazard for death, neither result was statistically significant.

**Caution!**

Multiple studies have shown that GC use prior to CHOP chemotherapy for canine and feline leukemia and lymphoma creates chemotherapy resistance and/or a reduced survival time even in patients that achieve a complete remission while on chemotherapy. The mechanism of GC-induced chemotherapy resistance is unknown, although it does not appear to be due to early induction of P-glycoprotein expression, which is commonly associated with chemotherapy resistance. Similarly, it is unknown when GC-induced resistance develops during treatment. It appears that the influence of GCs on remission times does not change if GCs are given for less than 2 weeks or for longer periods, suggesting resistance has already developed 2 weeks into a course of treatment and possibly much earlier.

Due to the effects of GCs on lymphocytes, it is also possible that GC use may make a definitive diagnosis of lymphoma difficult if cytologic samples are hard to interpret because of lymphocyte fragility. Although this has not been definitively proven to occur in veterinary medicine, it appears to be a problem for some types of lymphomas in humans.

Given these concerns, it is prudent to withhold GC treatment until a diagnosis of lymphoma is made and a treatment plan elected, except potentially in emergent cases (e.g., life-threatening hypercalcemia, tracheal obstruction due to lymph node enlargement).

**Mast Cell Tumors**

A variety of treatment options exist for canine and feline mast cell tumors (MCTs). Typically, treatment involves surgical removal, if possible, followed by adjuvant radiation therapy or chemotherapy as dictated by the location and aggressiveness of the tumor. GCs
are often part of the treatment plan, either neoadjuvantly to help shrink the tumor before surgery and control histamine release, or adjuvantly following surgical removal. The response rate of canine MCTs to systemic GCs alone ranges from 20% to 70%, supporting the use of GCs in treatment of MCTs.25-27 This wide response rate is likely due to the expression levels of GC receptors on neoplastic mast cells, where lower GC receptor expression has been associated with a decreased response or resistance to GC treatment.28 In addition, it has been shown that MCTs have some inherent drug resistance to GCs or develop GC resistance.29 The impact of previous GC use on MCT response to chemotherapy has not been examined, although anecdotally, previous GC use does not seem to significantly affect outcome.

Intralesional administration of GCs, specifically triamcinolone, has been reported in dogs with cutaneous MCTs.30 In one study, patients were treated with intralesional triamcinolone alone (n = 5); a combination of intralesional triamcinolone and systemic GCs (n = 6); or a combination of intralesional triamcinolone and cytotoxic chemotherapy, with or without systemic GCs and radiation therapy (n = 13). For those treated with triamcinolone only, 1 achieved a complete response, 3 had a partial response, and 1 had stable disease. Adverse events included local hemorrhage (n = 1) and suspected gastrointestinal (GI) ulceration (n = 2; one receiving oral GCs, one not). Thus, it was concluded that intralesional triamcinolone, with or without additional therapy, may be safe and effective for canine cutaneous MCTs.30

**Caution!**
If GCs are used prior to MCT surgery, it is recommended that the fur over the mass be shaved, and the mass circled using a Sharpie pen. Due to the relatively high response rate of MCTs to GCs, it is possible that the mass may disappear entirely between starting GCs and the day of surgery. Having the location of the tumor marked will help facilitate appropriate removal of the tumor.

**Multiple Myeloma**
Multiple myeloma is a rare hematopoietic tumor of malignant plasma cells that occurs in both dogs and cats. These malignant plasma cells, typically stemming from the bone marrow, produce an overabundance of a single type or portion of immunoglobulin (the M component), leading to hyperglobulinemia. The clinical signs of multiple myeloma are due to the high levels of circulating M component, neoplastic cell infiltration of bone or organs, or both. Clinical manifestations of multiple myeloma include discrete osteolytic lesions, hyperviscosity syndrome, renal disease, hypercalcemia, cytopenias, abnormal clotting times, and immunodeficiency. A diagnosis of multiple myeloma in dogs is based on the presence of neoplastic plasma cells in the bone marrow, lytic bone lesions, and serum or urine myeloma proteins.

In humans, GCs have been shown to have an antitumor effect in multiple myeloma and are an important part of single-agent and combination therapy.31 This approach has been extrapolated to treatment protocols successfully utilized in dogs and cats with multiple myeloma.7,32

**Caution!**
Hyperglobulinemia alone does not indicate a diagnosis of multiple myeloma. Lymphoma and tick-borne diseases also commonly present with hyperglobulinemia; therefore, it is important to complete a thorough workup to attain a correct diagnosis.

**Nonhematologic Cancers**
The treatment of nonhematologic cancers with GCs is more controversial. It appears that GCs, depending on the tumor type, may prevent tumor progression and metastasis, or may inhibit chemotherapy-induced cell apoptosis. These discrepant results are likely due to a multitude of factors, including different cell types of origin, varying GC receptor levels, the type of GC administered, and the dosage of GC administered.1

**The Good**
In human medicine, GCs alone have been shown to produce favorable outcomes in thymoma, breast, and prostate cancer. In breast cancer, GCs increase the response rate to chemotherapy and endocrine therapy when given in combination but do not influence overall survival.33 In vitro data suggest that GCs, through activation of the GC receptor, may reduce estrogen-induced cell proliferation in breast cancer and mitigate androgen receptor activation and expression in prostatic cancer, helping to suppress cancer cell growth in these 2 tumor types. For various types of GI cancer,
GCs alone were not found to influence survival times compared with placebo. Studies evaluating the combination of GCs and chemotherapy for GI cancer are mixed, implying a likely neutral effect.\textsuperscript{33}

Metastasis is responsible for 90% of cancer deaths, but adequate treatments for metastatic disease have not been thoroughly evaluated, including GCs.\textsuperscript{34} In vitro evaluations suggest that GCs suppress cancer cell migration and invasion through induction of E-cadherin or downregulation of matrix metalloproteinases 2 and 9, RhoA (Ras homolog family member A), and interleukin (IL)-6.\textsuperscript{1} Induction of microRNA, specifically miR-708, decreases cancer cell migration, adhesion, and abdominal metastasis through inhibition of Rap1B.\textsuperscript{35} In addition, various studies have implied that GCs suppress angiogenesis through downregulation of proangiogenic factors (IL-8 and vascular endothelial growth factor [VEGF]), preventing additional blood and nutrients from reaching the growing tumor.

**The Bad**

Despite the positive effects seen in breast cancer patients in vivo, in vitro evidence suggests that GCs can induce resistance when combined with radiation or chemotherapy in culture or mouse xenograft models. Many epithelial cancers have been shown to have this propensity, such as breast, ovarian, cervical, prostatic, testicular, urothelial, and pancreatic.\textsuperscript{1} This resistance is thought to be mediated through upregulation of mitogen-activated protein kinase phosphatase, serine/threonine survival kinase 1, and negative regulator of nuclear factor kappa B (NF-\textit{kappa}B), although this has not been supported in clinical patients.\textsuperscript{1}

While studies in human medicine generally have shown GCs to have a positive effect, or at least a neutral one, on patient outcome, in some instances GCs lead to less favorable outcomes or deleterious secondary sequelae. The use of GCs for primary central nervous system cancers is typically supported due to their effects on tumor-induced edema and subsequent neurologic deficits.\textsuperscript{36} However, there is evidence that GCs may exert only a neutral effect on the tumor and may cause significant adverse effects, including an increased risk of infection when combined with chemotherapy.\textsuperscript{33} In lung cancer, it appears that GCs decrease overall survival when used as monotherapy or in combination with chemotherapy.\textsuperscript{33} Given the information available, it has been recommended in human medicine to avoid high-dose continuous GCs in patients with nonhematologic malignancies, as this dosage decreases survival.\textsuperscript{33}

**Veterinary Medicine**

The use of GCs for nonhematologic cancers in veterinary medicine has not been thoroughly studied, either in vitro or in vivo. It is generally accepted that patients with central nervous system tumors benefit from prednisone, likely due to the effect on peritumoral edema,\textsuperscript{37} although the true impact and cellular changes induced by GCs in this and other nonhematologic malignancies are unknown.

**Caution!**

Given the lack of evidence for GC use in veterinary nonhematologic malignancies and the potential detrimental effects as evidenced in human malignancies, judicious use of GCs is recommended in any nonhematologic malignancy.

**Supportive Care**

Glucocorticoids are frequently used as an adjuvant to mitigate adverse events during chemotherapy and radiation therapy. In humans, GCs have been shown to increase appetite; decrease vomiting, nausea, and weight loss; reduce fatigue; decrease ureteric obstruction; and alleviate bone pain associated with metastasis.\textsuperscript{1} Anecdotally, and based on human studies, GCs are also used in veterinary medicine for many of these same reasons, especially to reduce GI effects from chemotherapy.\textsuperscript{38}

Despite the frequent use of GCs, the mechanisms through which they reduce nausea and vomiting have not been fully elucidated. In humans, several hypotheses exist: physiologically low levels of GCs have been linked to nausea and vomiting, which may be exacerbated during chemotherapy or radiation therapy treatment; anti-inflammatory effects may mitigate these GI signs, as other anti-inflammatory medications (e.g., cyclooxygenase [COX] inhibitors) appear to do; GCs have been shown to reduce serotonin production, blocking transmission of the vomiting response; and finally, GCs inhibit formation of other substances connected to the vomiting response, such as prostaglandin and substance P.\textsuperscript{4} The best use of GCs and their role in palliative treatment for dogs and cats with cancer have yet to be fully determined.
Limitations/Adverse Effects
The use of GCs in veterinary oncologic care is stymied by the potential adverse effects and subsequent effect on quality of life for patient and owner. In dogs, the most frequent adverse effects of systemic GCs have been reported to be polydipsia, polyuria, vomiting, diarrhea, and polyphagia. Less commonly reported adverse effects include panting, behavior changes, delayed wound healing, and iatrogenic hyperadrenocorticism (Cushing’s disease). Research also suggests that anti-inflammatory doses of oral GCs can potentially affect cardiac function in dogs, but not cats, due to an increase in blood pressure and cardiac afterload. Prednisolone-induced diabetes mellitus has been reported in about 10% of cats receiving high-dose prednisolone therapy (≥1.9 mg/kg/day for >3 weeks) but is rarely reported in dogs. Given the many potential adverse effects of GCs, thorough consideration for each individual patient should be undertaken prior to prescribing GCs for any dog or cat.

Resistance
While GC-induced resistance to chemotherapy or radiation therapy can be a concern, as discussed above, resistance to GCs can also develop, leading to reduction or loss of response. It appears the most common mechanism of GC resistance is misregulation of both pro- and anti-apoptotic factors, including BCL2 (B-cell lymphoma 2), BIM (BCL-2–like protein 11), and MCL1 (myeloid cell leukemia 1). Alternatively, general changes in transcription, repression of cell cycle genes, and alterations in GC receptor regulation may play a role in the development of resistance. Unfortunately, it appears that mechanisms of GC resistance are specific to tumor type, preventing one broad-spectrum approach to decreasing GC resistance.

NSAIDs IN CANCER

Scientific Basis
Inflammation, particularly chronic inflammation, has been shown to initiate cancer development through increased angiogenesis, the development of fibrosis, infiltration of mononuclear immune cells, and tissue destruction. Following initiation, inflammation has also been shown to influence progression and aggressiveness of certain cancers. Multiple malignancies have been shown to express phenotypes that mimic inflammatory cells as they grow and progress, driving cell migration, angiogenesis, and metastasis. Thus, reducing inflammation may provide an advantage in treating some malignancies.

Potential therapeutic targets for anti-inflammatory drugs include a myriad of cytokines and chemokines, NF-xB, VEGF, fibroblast growth factor receptors, and most commonly, COX-2. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to increase apoptosis and decrease migration of tumor cells, as well as potentially increase tumor sensitivity to other treatments. In addition, blockade of COX-2 decreases the incidence of human colorectal, breast, lung, bladder, and esophageal cancers.

Extrapolating from human medicine, many tumor types in veterinary medicine have been evaluated for the expression of COX-2 as a potential therapeutic target. It has been found that numerous cancers of epithelial origin express COX-2 (BOX 1), and thus a COX-2 inhibitor may play a therapeutic role. Interestingly, oral fibrosarcoma, histiocytic sarcoma, MCTs, and lymphoma in dogs, as well as cutaneous squamous cell carcinoma, pulmonary adenocarcinoma, intestinal carcinoma, lymphoma, and injection site sarcoma in cats, have not been shown to express COX-2.
However, expression of COX-2 does not necessarily correlate with prognosis, and its blockade will not automatically result in a prolonged survival time. A recent systematic review of the literature attempted to correlate expression of COX-2 and outcome. It found that in canine mammary carcinoma, melanoma, osteosarcoma, and renal cell carcinoma and in feline mammary carcinoma, urothelial cell carcinoma, and oral squamous cell carcinoma, significant evidence exists to support the conclusion that COX-2 expression is associated with decreased overall survival. However, significant bias was present in some of these studies, making sweeping generalizations about the effect of COX-2 inhibition on outcome difficult.

**COX-2 Inhibition**

COX-2 inhibition is typically achieved using NSAIDs (FIGURE 1), which ultimately prevent synthesis and cancer-driving effects (inhibition of apoptosis, simulation of angiogenesis, decreases in immunity, and promotion of cell proliferation) of prostaglandins. NSAIDs also result in inhibition of cell cycle arrest and metastasis, preventing cancer progression at various points of development. However, some in vitro work suggests that antitumor effects are likely not directly cytotoxic. In addition, the best NSAID to use has not been established, and while many studies have evaluated piroxicam alone, firocoxib, deracoxib, and carprofen may have therapeutic efficacy.

COX-2 inhibition and the inhibition of prostaglandin synthesis, while potentially preventing progression of certain tumor types, may have significant adverse effects. Prostaglandins protect the GI mucosa through decreased acid production and increased mucus production as well as regulate renal blood flow, especially during decreased renal perfusion; thus, prostaglandin inhibition can negatively affect the GI tract and kidneys. Although COX-2–selective drugs may diminish GI adverse events in healthy GI tissues, this selectivity does not mitigate renal or hepatic adverse events.

**Tumor Response to COX-2 Inhibition**

Although many tumors express COX-2, their responses to NSAID treatment vary widely and evaluation or proof of efficacy is lacking, often making NSAID use experimental instead of proven. TABLE 1 outlines published studies that evaluated NSAIDs in vitro or in vivo for their therapeutic effects. Many tumors that have been shown to express COX-2 have not been evaluated for their response to NSAID treatment. This is most interesting with regard to apocrine gland anal sac adenocarcinoma, for which NSAIDs are frequently recommended, but this recommendation is based on anecdotal evidence.

**EP<sub>4</sub> Inhibition**

Given the possible adverse events associated with NSAID use, alternative therapeutic strategies are appealing. COX-2 blockade prevents the production of prostaglandins, inhibiting both detrimental and homeostatic effects within the body (FIGURE 1).
Blockade of the cascade after the production of prostaglandins, at their receptors, may confer the same effects as COX-2 inhibition without significant GI or renal impact.

COX-1 and COX-2 produce prostanoids from arachidonic acid (FIGURE 1). These prostanoids exert their effects through various G protein–coupled receptors. Each prostanoid has its own corresponding receptor, with the exception of PGE₂ (prostaglandin E₂), which exerts its effects through 4 EP (E-type prostanoid) receptor subtypes: EP₁, EP₂, EP₃, and EP₄.⁹⁶ EP receptors help maintain homeostasis in the brain, kidney, vascular smooth muscle cells, and platelets. Chronic and acute pain signals are also transmitted, in part, through these receptors.⁹⁷ It has been found that in many species, the EP₄ receptor specifically drives pain associated with osteoarthritis, and blockade of the EP₄ receptor can lead to pain control.⁹⁸

It has now been shown that the EP₄ receptor is the primary driver of cancer signals and is associated with development and poor prognosis in several human cancers.⁹⁹ Recently, multiple canine cancers have also been shown to have increased mRNA expression of the EP₄ receptor (BOX 2). Interestingly, canine urothelial cell carcinoma had expression of the EP₄ receptor, but at levels that were less than normal bladder mucosa. The reasons for this finding are not well understood.¹⁰¹ Work evaluating feline cancers for expression of EP₄ receptor mRNA is ongoing.

Given the human literature and the fact that many canine cancers express the EP₄ receptor, use of an EP₄ receptor antagonist may be a novel therapeutic alternative to traditional NSAIDs.

Grapiprant (Galliprant; Elanco, elanco.com) is a prostaglandin receptor antagonist, part of the piprant drug class. It specifically blocks the EP₄ receptor

| TABLE 1 Summary of Published Literature Evaluating NSAIDs for Canine and Feline Malignancies That Have Been Shown to Express COX-2² | NSAID EFFICACY IN VITRO² | NSAID EFFICACY IN VIVO |
|---|---|---|---|---|
| TUMOR TYPE | NSAID alone | NSAID in combination with maximum tolerated dose chemotherapy | NSAID in combination with metronomic chemotherapy | NSAID in combination with radiation therapy ± other treatment modalities |
| CANINE | | | | |
| Apocrine gland anal sac adenocarcinoma | ✓ | | | |
| Mammary carcinoma | ✓⁵⁷,⁶¹ | ✓⁵⁵,⁶² | ✓⁵³,⁶⁴ | ✓⁶⁵ |
| Nasal carcinoma | ✓ | ✓⁵⁵,⁶⁶,⁶⁷ | ✓⁶⁵ | |
| Oral melanoma | ✓⁵⁷ | | ✓⁶⁹ | ✓⁶⁵ |
| Osteosarcoma | ✓⁵¹,⁶⁷,⁶⁸-⁷¹ | ✓⁵⁵ | ✓⁵⁶,⁷² | |
| Prostatic carcinoma | ✓⁵¹ | | ✓⁶⁶ | |
| Cutaneous squamous cell carcinoma | ✓⁵⁵ | | | |
| Oral squamous cell carcinoma | ✓⁵⁴ | ✓⁵⁵,⁷⁵ | ✓⁶⁶,⁷⁶ | |
| Urothelial cell carcinoma | ✓⁵⁰,⁵⁷,⁷⁷ | ✓⁵⁵,⁷⁸-⁸⁰ | ✓⁵⁴-⁵⁶ | ✓⁹¹,⁹² |
| FELINE | | | | |
| Oral squamous cell carcinoma | ✓⁵⁴ | | ✓⁵¹,⁹⁴ | |
| Urothelial cell carcinoma | ✓⁵⁵ | | | |

*Canine intestinal carcinoma, meningioma, renal carcinoma, digital squamous cell carcinoma, and cutaneous hemangiosarcoma and feline mammary carcinoma have been found to express COX-2, but no literature evaluating NSAIDs in these tumors has yet been published.
²Alone or in combination with other treatment modalities.
COX=cyclooxygenase; NSAIDs=nonsteroidal anti-inflammatory drugs.
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in dogs with osteoarthritis. Safety data in cats are also available, although efficacy has yet to be established. Theoretically, if many cancers develop through inflammatory signals via PGE2 and the EP4 receptor, and the EP4 receptor is expressed or overexpressed on cancer cells, grapiprant may be an attractive alternative therapeutic option for many cancers that respond to NSAIDs.

Although grapiprant should be better tolerated than classical NSAIDs, adverse events can still occur. Those seen most frequently in dogs include mild vomiting, diarrhea, inappetence, and lethargy. These GI effects are typically short lived and self-limiting and rarely require supportive care. No changes to liver or kidney function have been noted in dogs treated with grapiprant. Cats also appear to tolerate grapiprant well, at least in short-term studies.

Conclusion

Gluocorticoids and NSAIDs can be potent primary or adjuvant treatments for a variety of cancers in veterinary medicine. Caution is required to balance the potential adverse effects on the patient and the control of the tumor. The role of GCs in the progression of some cancers is of particular concern and should not be overlooked when determining the role of GCs for a particular patient.

References


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The Role of Glucocorticoids and NSAIDs in Cancer Treatment for Dogs and Cats

TOPIC OVERVIEW
This article describes the uses of glucocorticoids and NSAIDs in veterinary oncology.

LEARNING OBJECTIVES
After reading this article, participants will be able to explain the scientific basis for use of glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs) in veterinary oncology. In addition, they will be able to give examples of specific tumors for which glucocorticoids or NSAIDs are potentially effective treatments.

1. Which of the following statements about glucocorticoid use in canine lymphoma is true?
   a. Glucocorticoids cause apoptosis of lymphoid cells.
   b. Glucocorticoids confer a longer survival time for dogs with B-cell lymphoma.
   c. Previous glucocorticoid use does not affect overall survival time.
   d. Previous glucocorticoid use does not affect achieving an accurate diagnosis of lymphoma.

2. Mast cell tumor response to glucocorticoids ranges from 20% to 70% because some mast cell tumor cells have _______.
   a. Increased glucocorticoid efflux pumps
   b. Decreased glucocorticoid receptor density
   c. Glucocorticoid receptors
   d. Decreased glucocorticoid transmembrane pumps

3. Which of the following statements is/are true regarding glucocorticoids and solid malignancies?
   a. Glucocorticoids can suppress angiogenesis.
   b. Glucocorticoids can decrease cancer cell migration.
   c. Glucocorticoids can decrease the formation of abdominal metastatic disease.
   d. All of the above

4. Which of the following statements about the use of glucocorticoids for central nervous system cancers is true?
   a. Glucocorticoids cause apoptosis of central nervous system cancer cells.
   b. Glucocorticoids decrease metastatic spread.
   c. Glucocorticoids decrease tumor-induced edema.
   d. Glucocorticoids decrease lymphangiogenesis.

5. In humans, when used as supportive care, glucocorticoids have been shown to _______.

   a. Increase appetite
   b. Decrease vomiting
   c. Decrease weight loss
   d. All of the above

6. Which of the following is not a known driver of chronic inflammation in cancer development?
   a. Decreased angiogenesis
   b. Fibrosis development
   c. Tissue destruction
   d. Infiltration of mononuclear immune cells

   a. True
   b. False

8. Which of the following tumors has been shown to express COX-2 and respond favorably to NSAID therapy?
   a. Intestinal carcinoma
   b. Digital squamous cell carcinoma
   c. Urothelial cell carcinoma
   d. Meningioma

9. Which of the following prostanoid receptors is thought to contribute most to neoplasia development?
   a. EP1
   b. EP4
   c. IP
   d. FPα

10. Which of the following canine cancers might respond to grapiprant based on positive prostanoid receptor expression?
    a. Apocrine gland anal sac adenocarcinoma
    b. Renal carcinoma
    c. Glioblastoma
    d. Oral squamous cell carcinoma