ASK A SPECIALIST

Top Questions About Cancer From General Practitioners

***Joanne Intile**, DVM, DACVIM (Oncology), and **Jake Romeiser**, DVM*
North Carolina State University College of Veterinary Medicine, Raleigh, North Carolina

Oncology is a broad field, with multiple types of cancer requiring varied diagnostic and therapeutic approaches. Covering the details associated with all types of cancer, or even the details associated with 1 type of cancer, is outside the scope of this article. This article instead focuses on general questions commonly asked about mast cell tumors, lymphoma, corticosteroids versus nonsteroidal anti-inflammatories, and chemotherapy.

MAST CELL TUMORS

What can prevent the development of multiple cutaneous mast cell tumors?

Unfortunately, nothing prevents the development of multiple cutaneous mast cell tumors. Mast cell tumors require surgery unless proven otherwise (e.g., metastatic tumors, high-grade tumors). The need for surgical tumor removal applies to dogs with multiple tumors that develop over months or years as well as those with synchronous tumors (tumors appearing within days or weeks of each other).

When multiple low-grade tumors are adequately controlled by surgery, many dogs can survive normal lifespans. Therefore, the optimal plan is to remove and grade the tumors as each tumor is thought to arise independently and biological behavior can vary.

A nonsurgical/nonchemotherapeutic option for treating mast cell tumors in dogs is tigilanol tiglate (Stelfonta; Virbac, vet-us.virbac.com). Tigilanol tiglate is injected directly into the tumor, causing cell death and leaving a wound that heals by second intention (average healing time, 4 to 6 weeks). Tumors must meet specific criteria (size, location, metastasis) for treatment to be effective. After 1 injection, 75% of tumors respond, and after

Abstract

Diagnosing and treating cancer can be challenging, but small animal general practitioners should be prepared when a patient is diagnosed with cancer. This article aims to answer questions that general practitioner veterinarians commonly ask oncologists and to assist general practitioners with treating and referring oncology patients.

Take-Home Points

- Development of multiple cutaneous mast cell tumors cannot be prevented, but there are surgical and nonsurgical treatment options.
- Using prognostic panels for canine mast cell tumors to predict the risk for recurrence or spread of grade 2 tumors can be challenging, but their use may help predict the behavior of tumors showing conflicting histopathologic features.
- Before lymphoma patients are referred to oncology specialists, testing (e.g., fine-needle aspiration, cytology) is recommended.
- Before lymphoma patients are treated, a confirmed diagnosis, laboratory work, staging, and immunophenotyping are recommended.
- Corticosteroids can be used to treat lymphoma, mast cell disease, and plasma cell disease; nonsteroidal anti-inflammatory drugs can be used to reduce pain and inflammation and may also have anticancer properties.
- Chemotherapy is generally well tolerated by most patients, but individual tolerance varies according to multidrug resistance mutation status, patient size, presence of renal/hepatic insufficiency, and other concurrent illnesses.

2 injections, 87% respond.[1] A study that evaluated dogs with multiple mast cell tumors found that 81% had a complete response.[2] One year after treatment with tigilanol tiglate, 90% of dogs have remained tumor free.[3] A downside to treatment with tigilanol tiglate is that the histologic grade of the tumor cannot be determined. Due to labeling restrictions, treating more than 1 tumor at a time is not recommended, and there is a maximum volume of this drug that can be injected.

When do oncologists recommend using prognostic panels for canine mast cell tumors?

Despite attempts to simplify tumor grading, veterinary oncologists still find it challenging to predict the risk for recurrence or spread of grade 2 tumors, whether they are high or low grade. The prognostic panel available through the Michigan State University Veterinary Diagnostic Laboratory evaluates tumor parameters (including proliferation markers Ki-67 [antigen Kiel 67] and AgNORs [argyrophilic nucleolar organizer regions], PCR to detect internal tandem duplication mutations in exons 11 and 8 of the *c-Kit* gene, and *KIT* gene immunohistochemistry) to analyze the cellular localization of the tyrosine kinase receptor. Results offer in-depth insight into the biological behavior of mast cell tumors and help identify those that may exhibit more aggressive behavior. The authors use the prognostic panel to support the monitoring of incompletely excised grade 2 low-grade tumors with favorable prognostic panel scores and to recommend chemotherapy for completely excised grade 2 high-grade tumors with unfavorable prognostic panel scores.

Prognostic panels also influence the authors' approach to tumors that exhibit conflicting biological behavior (e.g., grade 2 low-grade tumors with a history of rapid growth) or are in anatomic locations considered high risk (e.g., perineal, inguinal). The panels can be used to help predict the behavior of tumors showing conflicting histopathologic features (e.g., low mitotic count with concurrent marked alterations in cellular morphology) and for dogs with mitotic counts that are borderline between low and high (mitotic count, 5 to 7).

When there is already evidence of aggressive behavior (e.g., grade 3 high-grade tumors, known metastatic tumors), prognostic panels are not helpful because regardless of results, aggressive treatment is warranted.

LYMPHOMA

Which diagnostic tests should be performed when lymphoma is suspected and how soon before referral?

Before an oncologist is consulted, several diagnostics can be performed to streamline care, provide prognostic information, and positively affect patient outcomes. The first step is obtaining a definitive diagnosis. Approximately 80% of dogs with lymphoma have multicentric lymphoma, which is readily diagnosed with fine-needle aspiration and cytology.[4] Obtaining a diagnosis before consulting with an oncologist can speed up treatment and give clients more time to process their pet's condition. Referral is appropriate for dogs with suspected lymphoma in hard-to-reach areas (e.g., mediastinum, gastrointestinal [GI] tract).

However, pretreatment with steroids may hinder the ability to obtain a definitive diagnosis.

The authors recommend examining samples in-house to ensure they are of adequate diagnostic quality before submitting them for analysis by a clinical pathologist. Veterinarians can save themselves time and money by looking at 1 or 2 slides to be sure they accurately sampled the lymph node (i.e., not the salivary gland or fat). If cytologic samples are not diagnostic, additional samples can be obtained while the patient is still in the clinic. If, after multiple attempts, the samples are still not diagnostic, surgical biopsies are recommended.

What is the minimum information needed to treat lymphoma?

At the authors' institution, the minimum information required to institute treatment is a diagnosis of lymphoma and baseline laboratory work (CBC reviewed by a pathologist, chemistry panel, urinalysis). Laboratory work may need to be rechecked, depending on the time between consultation and referral. The duration varies according to oncologist preference and case history.

A definitive diagnosis of lymphoma can be complicated by corticosteroid treatment, which can induce apoptosis and alter the morphology of remaining lymphocytes, making it challenging to differentiate between reactive changes and lymphoma. Corticosteroids can also mask clinical signs of lymphoma (e.g., swelling, lymphadenopathy), which complicates the interpretation of staging tests. If immediate treatment is required (e.g., hypercalcemic patients, severely ill patients), collecting diagnostic samples beforehand to ensure accurate diagnosis and effective treatment planning is essential.

An oncologist can use staging tests to track treatment response and monitor changes resulting from chemotherapy or disease progression.

What are the benefits of staging tests?

Before treatment of lymphoma, staging and immunophenotyping are ideal. Thorough staging involves a CBC, chest radiography, abdominal ultrasonography, and bone marrow aspirate and provides essential information for monitoring and prognosis. An oncologist can use staging tests to track treatment response and monitor changes resulting from chemotherapy or disease progression. Given that lymphoma often affects older dogs that may have other cancers, thorough staging helps provide a comprehensive view of the patient's health and supports informed treatment choices. If cost is a concern, immunophenotyping should be prioritized because it most significantly affects prognosis and treatment decisions. Immunophenotyping can be performed before referral by using flow cytometry, PARR (PCR for antigen receptor rearrangement), or immunocytochemistry of lymph node aspirates.

TREATMENT WITH CORTICOSTEROIDS VERSUS NSAIDs

When should I reach for an NSAID versus a steroid for a patient with cancer?

Corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) are valuable tools for treating cancer, but they are not interchangeable and indications for their use differ.

Corticosteroids are used to treat lymphoma, mast cell disease, and plasma cell disease. They are directly cytotoxic to lymphocytes and mast cells and can inhibit mast cell proliferation.[5,6] They can also decrease tumor-associated inflammation and edema. Side effects of corticosteroids can be beneficial for cancer patients. For example, polyuria and increased renal calcium excretion can help manage hypercalcemia of malignancy. In addition, corticosteroids can increase appetite and energy levels, which are helpful during palliative or hospice care. Even if corticosteroids do not have a direct anticancer effect, such off-target effects may still be beneficial.

NSAIDs are effective for reducing pain and inflammation and may also have anticancer properties. They work by blocking cyclooxygenases (COXs), inhibiting angiogenesis, and slowing tumor

progression.[7] Many tumor types overexpress COX, but the anticancer activity of NSAIDs has been demonstrated in only a few clinical models.[8] Although published data are promising, most studies involved NSAIDs as part of a combination therapy with other treatments. Therefore, determining the true efficacy of NSAIDs as a stand-alone treatment remains challenging. The analgesic and anti-inflammatory properties of NSAIDs are crucial for improving the quality of life for many veterinary cancer patients. For more information, see **go.navc.com/4ilpyOM**.

CHEMOTHERAPY

What evidence-based information describes the risk for chemotherapy adverse effects, and does that information apply to my patient?

Chemotherapy is generally well tolerated, and when adverse effects occur, they are most often mild and self-limiting. Successful management of cancer involves discussing with clients the potential for benefit, toxicity, and cost (e.g., financial, time, effect on human–animal bond). Before starting chemotherapy, consider factors like the client's difficulty administering medication at home, the stress of hospital visits, and potential challenges posed by travel to and from the veterinary clinic. These factors and any preexisting health conditions can affect the patient's quality of life; however, chemotherapy can be stopped at any time if there is concern about tolerability and adverse effects.

Chemotherapy-induced adverse events are graded from 1 to 5 according to the Veterinary Cooperative Oncology Group consensus statement,[9] with 1 being mild and 5 being death. Toxicities with a grade of 3 or higher are considered clinically significant. The most common adverse events are myelosuppression and GI toxicity.

Interpreting studies of risk can be complex. Even if the overall numerical risk of an adverse event is high, its clinical effect might be minimal. For instance, neutropenia might develop while the patient remains asymptomatic and healthy unless they experience an infection. In 1 study, adverse events affected 80% of dogs (124/155); severe adverse events (defined as any grade 4; any symptomatic grade 3 hematologic adverse event; or adverse events leading to the cessation of treatment, hospitalization, or death) affected 30%.[10] Of note, the authors of this study did not use prophylactic medications, which are known to mitigate the risk for myelosuppression and GI events. For example, use of maropitant in dogs and mirtazapine in cats has been shown to mitigate the onset of GI adverse events.[11,12] Trimethoprim-sulfadiazine has decreased hematologic and nonhematologic toxicity in dogs with osteosarcoma and lymphoma patients receiving chemotherapy.[13]

Another study, which aligns more with the authors' experience, reported grade 1 adverse events in 83% of patients; higher-grade adverse events (grade ≥ 2) affected only about 20% of patients.[14] Anecdotally, oncologists report that 70% of veterinary patients have no clinical adverse event in response to chemotherapy; 20% to 25% have mild self-limiting side effects that can improve with outpatient management; and only 5% to 10% experience severe, dose-limiting adverse effects resulting in hospitalization, with grade 5 adverse events (death) occurring in ≤ 1% of treated patients.

With regard to an individual patient's general risk for adverse events, the risk can be influenced by patient-specific characteristics such as multidrug resistance mutation status, patient size, presence of renal/hepatic insufficiency, and other concurrent illnesses.

SUMMARY

The 2 most common types of tumors in dogs are multiple cutaneous mast cell tumors, which cannot be prevented but for which treatment options exist, and lymphoma, which is best treated after completion of diagnosis, laboratory work, staging, and immunophenotyping. Corticosteroids and NSAIDs are useful cancer treatments, but they are not interchangeable and their indications differ. Chemotherapy is generally well tolerated; any adverse effects are usually mild and self-limiting, and if not, chemotherapy can be stopped at any time. TVP

References

1. De Ridder TR, Campbell JE, Burke-Schwarz C, et al. Randomized controlled clinical study evaluating the efficacy and safety of intratumoral treatment of canine mast cell tumors with tigilanol tiglate (EBC-46). *J Vet Intern Med*. 2021;35(1):415-429. doi:10.1111/jvim.15806
2. Brown GK, Finlay JR, Straw RC, et al. Treatment of multiple synchronous canine mast cell tumours using intratumoural tigilanol tiglate. *Front Vet Sci*. 2022;9:1003165. doi:10.3389/fvets.2022.1003165
3. Jones PD, Campbell JE, Brown G, Johannes CM, Reddell P. Recurrence-free interval 12 months after local treatment of mast cell tumors in dogs using intratumoral injection of tigilanol tiglate. *J Vet Intern Med*. 2021 ;35(1):451-455. doi:10.1111/jvim.16018
4. Ponce F, Marchal T, Magnol JP, et al. A morphological study of 608 cases of canine malignant lymphoma in france with a focus on comparative similarities between canine and human lymphoma morphology. *Vet Pathol*. 2010;47(3):414-433.

doi:10.1177/0300985810363902

5. Smith LK, Cidlowski JA. Glucocorticoid-induced apoptosis of healthy and malignant lymphocytes. *Prog Brain Res*. 2010;182:1-30. doi:10.1016/S0079-6123(10)82001-1
6. Takahashi T, Kadosawa T, Nagase M, et al. Inhibitory effects of glucocorticoids on proliferation of canine mast cell tumor. *J Vet Med Sci*. 1997;59(11):995-1001. doi:10.1292/jvms.59.995
7. Doré M. Cyclooxygenase-2 expression in animal cancers. *Vet Pathol*. 2011;48(1):254-265. doi:10.1177/0300985810379434
8. Musser ML.The role of glucocorticoids and NSAIDs in cancer treatment for dogs and cats. *Todays Vet Pract*. 2022;12(3):54-65.
9. LeBlanc AK, Atherton M, Bentley RT, et al. Veterinary Cooperative Oncology Group-Common Terminology Criteria for Adverse Events (VCOG-CTCAE v2) following investigational therapy in dogs and cats. *Vet Comp Oncol*. 2021;19(2):311-352. doi:10.1111/vco.12677
10. Chavalle T, Chamel G, Denoeux P, et al. Are severe adverse events commonly observed in dogs during cancer chemotherapy? A retrospective study on 155 dogs. *Vet Comp Oncol*. 2022;20(2):393-403. doi:10.1111/vco.12782
11. Rau SE, Barber LG, Burgess KE. Efficacy of maropitant in the prevention of delayed vomiting associated with administration of doxorubicin to dogs. *J Vet Intern Med*. 2010;24(6):1452-1457. doi:10.1111/j.1939-1676.2010.0611.x
12. Lee CH, Wang SL. Oral mirtazapine decreases the gastrointestinal adverse effects in cats on doxorubicin chemotherapy. *Vet J*. 2024;304:106087. doi:10.1016/j.tvjl.2024.106087
13. Chretin JD, Rassnick KM, Shaw NA, et al. Prophylactic trimethoprim-sulfadiazine during chemotherapy in dogs with lymphoma and osteosarcoma: a double-blind, placebo-controlled study. *J Vet Intern Med*. 2007;21(1):141-148. doi:10.1892/0891-6640(2007)21[141:ptdcid]2.0.co;2
14. Cunha SCS, Silva FBF, Corgozinho KB, Silva KVG, Ferreira AMR. Adverse effects of chemotherapy in dogs. *World Vet J*. 2017;7(3):74-82. http://dx.doi.org/10.5455/wvj.20170896

Joanne Intile

Dr. Intile completed her DVM degree at Cornell University and her rotating internship in small animal medicine and surgery at Long Island Veterinary Specialists. She returned to Cornell for her residency in medical oncology and then worked in private specialty practices. Dr. Intile's time as an adjunct instructor at Suffolk County Community College solidified her career goal of working in academia. She joined the faculty of the North Carolina State University College of Veterinary Medicine in 2017.

Jake Romeiser

Dr. Romeiser completed his DVM degree at the Virginia-Maryland College of Veterinary Medicine. He is a second-year medical oncology resident at North Carolina State University and previously completed a small animal rotating internship at BluePearl Franklin in Tennessee and a medical oncology specialty internship at North Carolina State University. His primary clinical interest is treating hematopoietic neoplasia, such as lymphoma and leukemia.