Chemotherapy for the private practitioner/oncology potpourri

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Chemotherapy for the private practitioner

Based on conversations with private practitioners over the years, I appreciate that many owners of tumor-bearing animals are not interested in referral to an oncologist for treatment but might consider treatment if available without travel. Chemotherapy, with some limits, is within reach of many veterinarians and opens up possibilities for treating patients for which referral can't happen. For the purposes of this discussion, oral chemotherapy will encompass dedicated chemotherapy drugs, but not glucocorticoids or non-steroidal anti-inflammatory drugs (NSAIDs); NSAIDs are used, some might say promiscuously, by oncologists for their potential anti-tumor benefits, low risk of adverse effects, and ease of administration by owners. For many patients, the risk-potential benefit analysis would conclude that NSAIDs are a reasonable treatment in lieu of no treatment at all whether there is proven benefit in the population or not.

It should be noted up front that clinicians wanting to use chemotherapy drugs should become knowledgeable regarding indications and contraindications, metabolism/excretion, toxicity, and management of toxicity/adverse effects to safely incorporate these agents into one's practice. One should also become familiar with methods to minimize the potential health hazard that chemotherapy, or its metabolites, pose to people.

There are two basic strategies to consider when contemplating chemotherapy for tumor bearing animals: cytotoxic (high dose) chemotherapy, or metronomic (low dose) chemotherapy. The goal of cytotoxic chemotherapy is to directly kill tumor cells with the chemotherapeutic agent; the goal of metronomic chemotherapy is to indirectly kill tumor cells, or limit tumor growth. Either strategy can be used with other treatment approaches, likely surgery in general practice (as opposed to radiation therapy). With either strategy, the agents most likely to be used are orally administered drugs which offer the advantage of keeping the drugs out of one's hospital (limiting human exposure) and making treatment easier for many owners. Chemotherapy drugs can be prescribed through various pharmacies, and in some instances, doses can be compounded to make dosing accurate for an individual animal; compounding can, for some drugs, reduce the cost of treatment, but does create a degree of uncertainty regarding the delivery of the actual dose as prescribed. Still, many oncologists routinely use compounding pharmacies to facilitate appropriately dosing a given patient.

The most commonly used oral chemotherapeutic drugs are cyclophosphamide, chlorambucil, lomustine, and toceranib (Palladia). Cyclophosphamide and chlorambucil are often used in metronomic protocols, although they are used for cytotoxic treatment in some cases. There are other orally administered chemotherapy drugs, but compared to the above, the others tend to have more limited indications and are thus considered for a smaller proportion of tumor-bearing animals.

Metronomic chemotherapy protocols typically incorporate administration of low daily doses of chlorambucil or cyclophosphamide in conjunction with an NSAID; some oncologists have other drugs that they might use in a metronomic manner. Metronomic chemotherapy checks many boxes that make it appealing to clients: drugs are given at home, the risk of adverse effects is low and less monitoring is needed, and costs are typically less over a period of treatment than for cytotoxic doses. For many patients, the doses of the drugs will need to be compounded as hinted at above. Owners need to be aware that animals treated with such approaches will be eliminating chemotherapy drugs or metabolites at presumably low concentrations in urine, or potentially stool or vomit. There are no studies that have quantitated amounts of chemotherapy or metabolites excreted by treated animals, and while the risk to

people is not known, routine chemotherapy precautions (wearing gloves when cleaning up accidents or handling medications, limiting exposure to children or immunocompromised individuals) are recommended while pets in the house are treated in this manner. Because of this potential risk, the author has had clients that have declined administration of chemotherapy to their animals to eliminate an avoidable risk of DNA damage (chemotherapy drugs can themselves be carcinogenic) in their children.

The mechanisms of action underpinning metronomic chemotherapy are decreased vasculogenesis and fostering an environment in which anti-tumor immune responses may develop. As such, the approach is better for solid carcinomas and sarcomas of many types and is not well-suited to hematopoietic/lymphoid malignancies. Common tumor types for VTH patients treated with metronomic chemotherapy include soft-tissue sarcomas, hemangiosarcoma, oral melanoma, and carcinomas for which there are no other established medical options. There is also a chlorambucil-based protocol for the treatment of mast cell tumors in dogs.

For many patients with gross disease for which surgery or radiation therapy are not feasible, the goal of metronomic chemotherapy is to slow progression of the tumor and make the patient's tumor something that can be lived with. This essentially turns some tumors into chronic diseases with few quality of life consequences to the patient. As with other cancer treatments, there are no guarantees of benefit or treatment efficacy, the the duration of benefit, if seen, can't be predicted, but we have had some patients come to the point of stable disease for many months (or occasionally more) after a history of steady progression of their tumor.

Between the two approaches (cytotoxic, metronomic) to chemotherapy, many tumor types become amenable to treatment by general practitioners for owners not wanting to seek care from an oncologist.

Table: Oral chemotherapy drugs and common tumors treated with the drug

Cyclophosphamide	Toceranib (Palladia)
lymphoma	mast cell tumor
multiple myeloma	anal sac adenocarcinoma
many (metronomic)	gastrointestinal stromal tumor (GIST)
	thyroid carcinoma
	neuroendocrine tumors
Lomustine	chemodectoma
lymphoma	insulinoma
mast cell tumor	renal carcinoma
histiocytic sarcoma	oral squamous cell carcinoma (cats)
	others (as part of a metronomic protocol)
Chlorambucil	
Chronic leukemia	
Lymphoma	
Many (metronomic)	

Oncology potpourri

Electrochemotherapy, immunotherapy

Some treatments that some may not be aware of that are available at the VTH, or other institutions, include electrochemotherapy and immunotherapy. Electrochemotherapy involves administration of a chemotherapy agent, usually bleomycin, either into a tumor or surgical scar, or sometimes intravenously, followed by application of electrical pulses of a duration and wave-form to create openings/pores in cell membranes. Once the cell membrane is permeable, chemotherapy drugs move into the cell down a concentration gradient, and after a few minutes, the pores close to trap the drug into the cell. Patients eligible for ECT are typically those that have had a tumor surgically removed with “dirty” margins, and so ECT is an alternative to radiation therapy in some patients. Side effects associated with ECT are few, with local reactions or tissue injury the most common; systemic side effects from the chemotherapy drug are very uncommon. Mast cell tumors (minimal or microscopic disease) are arguably the most common tumor treated at the VTH with this approach, but a variety of tumor types, including sarcomas and carcinomas, have been described in the literature as treated successfully with ECT. A common protocol is two administer two sessions of ECT 2-3 weeks apart and evaluate the patient approximately a month after the second treatment to determine local tumor status and either monitor or treat with additional ECT sessions. Dogs with acanthomatous ameloblastoma of the oral cavity are candidates for ECT but often require more treatments to accomplish tumor resolution. Patients are treated with ECT on an outpatient basis and are discharged soon after treatment has been completed. Brief general anesthesia is needed for patient comfort.

Immunotherapy treatments for osteosarcoma is getting attention. A recent paper described the use of an autologous vaccine from patients’ tumors as providing outcomes comparable to amputation and chemotherapy. The approach is time and labor intensive requiring the isolation of patient T cells and in vivo and in vitro priming; it is also expensive. Torigen offers, for a fee, the generation of an autologous vaccine from a patient’s tumor. There is one published paper on their approach in hemangiosarcoma-bearing dogs, although Torigen will generate vaccines to other tumor types. There have not been published papers describing efficacy for tumors other than hemangiosarcoma, but the vaccines seem, so far, to be safe with few adverse effects. There is currently a non-funded clinical trial at WSU involving administration of a vaccine to the epidermal growth factor receptor (EGFR) to osteosarcoma dogs that have had limb amputation and chemotherapy or palliative radiation. One paper described a benefit (reduction in metastatic tumor volume) in dogs getting this vaccine. Like any vaccine-based strategy for nearly any disease, there are likely to be animals that benefit, and animals that don’t.

Liquid biopsy

Liquid biopsy, that is testing for tumor in blood, urine, or other fluids, is gaining substantial interest in both human and veterinary medicine for its potential as a non-invasive technique for the diagnosis of cancer. There are several platforms of liquid biopsies for dogs, including one based on nematode olfaction. All look for a different fingerprint or marker of cancer. None of the tests are 100% sensitive, meaning that there are false negative results, the proportion of which vary with the platform. Specificity figures often seem good, but there are caveats. For some, it is not clear whether the test would be superior to a good physical examination in terms of tumor detection.

Arguably the best established test is the detection of BRAF mutations in urine of dogs with urothelial carcinoma (formerly transitional cell carcinoma); it has a solid place as one of several diagnostic tests in dogs suspected of urothelial carcinomas. However, the user should be aware that there are surprisingly

few studies of the BRAF test that include more than just a few dogs with non-neoplastic lower urinary tract disease, such as chronic infection/inflammation, the population most likely to have overlap in clinical signs with dogs with urothelial carcinoma. Thus, one should be cautious with the interpretation of a positive test result in a patient with no clinical signs of lower urinary tract disease or without imaging (usually ultrasonographic) evidence of a mass in the bladder. Urothelial carcinoma can be confined to the prostate or urethra in some patients making a rectal examination an imperative element of a physical examination for a patient with a positive BRAF test but no evidence of a bladder mass. A rectal examination can be extended into a prostatic or urethral massage and collection of a voided urine sample for cytology to help provide additional support for the diagnosis of urothelial carcinoma.

Other strategies for liquid biopsies are being touted, in part, as a means for early cancer detection, but whether there are clinically important benefits- beyond simply making a cancer diagnosis- to be realized has yet to be demonstrated. As such tests inevitably become increasingly available, some of the questions that consumers (DVMs, owners) will have to bear in mind include:

- Will there be a survival benefit to early detection? Survival figures for screening tests could be subject to what is referred to as lead time bias, an inflation of survival time based solely on early diagnosis when compared to survival established from the onset of clinical signs.
- Is there an effective treatment to be implemented at the time of tumor diagnosis? For some tumor types, early diagnosis may not matter if there are not good treatment options.
- Where does the balance tip between implementation of treatment that risks morbidity/mortality in a patient that has no clinical signs of the tumor when the tumor is detected? As veterinarians, we are understandably cautious about implementation of treatment that may have a greater impact on a patient's quality of life than the disease being treated, and early cancer detection may make these waters a bit muddier.
- Will there be a negative consequence to the patient because of the diagnosis of "pseudo-disease?" Pseudo-disease in this case is a tumor that is not likely to, or won't, negatively affect the patient because the tumor progresses slowly, or not all.

The liquid biopsy approaches are likely to also play an important role for some patients in tumor monitoring but given the current technology and limits of sensitivity for the detection of small tumor burdens, there may be hurdles to reliance on liquid biopsies for tumor monitoring at this time.

Until such time that there is data showing clear-cut clinical benefits, ideally from prospective studies of the use of liquid biopsies in populations of tumor-bearing patients and patients with non-neoplastic disease but clinical signs that overlap with neoplasia, it is the opinion of the author that liquid biopsies should be carefully used.

References available upon request.