PBGV Health Watch

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This series of informative articles is for those interested in learning more about the health of the PBGV breed.

Cancer Care in Cats and Dogs

The pace of progress in veterinary oncology over the last 5 to 10 years has been nothing short of astounding. There is a new focus on treatments specifically designed for cats and dogs, rather than simply adapting human protocols to veterinary species. Many of these new therapies are possible due to advances in our knowledge of cancer genetics and molecular biology. In addition, the recognition of similarities in the biology of veterinary and human cancers has fueled the field of comparative oncology and provided opportunities to benefit both pets and their people. The combination of expanding knowledge of cancer biology and the feasibility of using sophisticated technologies in veterinary oncology has provided new treatment options for cats and dogs with cancer.

Surgery. Although many recent advances in cancer treatment are in the realm of medical therapy, surgery continues to be the first-line treatment for most localized cancers. Surgery provides certain clinical benefit when a tumor can be resected completely. It affords the additional advantage of providing large tissue samples for histopathologic examination that can confirm a diagnosis as well as provide important prognostic information.

Radiation Therapy. Once available at only a handful of sites, radiation therapy for veterinary cancer patients has become both more accessible and more sophisticated. The most common use of radiation therapy is control of microscopic residual disease when a tumor cannot be removed completely with surgery. However, radiation therapy is also applied to bulky tumors with either definitive (i.e., curative) or palliative intent. The most common form of radiation therapy in veterinary medicine is megavoltage (high-energy), external beam radiotherapy. This typically involves the use of a linear accelerator that generates a beam of either photons or electrons that ultimately damages DNA of exposed tissue within the radiation field. Radiation therapy exploits the relative inefficiency of DNA repair in tumor cells compared to normal tissues. To enhance the anticancer effect while minimizing complications in normal tissues within the radiation field, radiation therapy is typically delivered as multiple small doses given on a daily basis over three to five weeks. For palliative protocols, a single, larger fraction may be given once a week for three to four treatments.

Recent advances in radiation therapy include the use of highly precise intensity modulated radiation therapy (IMRT) and stereotactic radiosurgery (SRS). IMRT uses multileaf collimators to shape the photon beam emanating from the linear accelerator. In addition, many small beams of radiation are delivered at different angles. The result is a radiation field that conforms to the precise shape of the tumor, thereby sparing adjacent sensitive structures, such as the spinal cord or normal brain. Stereotactic radiosurgery is often delivered as a single high dose of radiation. The term radiosurgery seems to be a misnomer as no cutting is involved. However, the dose of radiation delivered is large enough that it results in ablation of the irradiated tissue. Precise delineation of the tumor through advanced imaging (CT scan or MRI) and meticulous patient positioning is crucial for these techniques. In many cases, a patient frame is needed, although fiducial tracking with markers and imagine guidance systems can be used to ensure accurate delivery of the radiation.

IMRT and SRS have largely been used to treat tumors involving the central nervous system in people. In veterinary medicine, there are published reports on the use of SRS in the treatment of brain masses in dogs, canine appendicular osteosarcoma and pituitary tumors in cats.

Conventional Chemotherapy. Conventional chemotherapy is gaining greater widespread acceptance among pet owners and veterinarians as a mainstream treatment for dogs and cats with cancer. This is likely due to increased recognition that pets generally tolerate these treatments well. For the most part, chemotherapy regimens used in veterinary oncology practices are adopted from human protocols, using agents in extra-label fashion. However, there are signs that this may be changing as pharmaceutical companies are beginning to show interest in seeking FDA approval for veterinary indications of new and existing chemotherapy agents.

Conventional cytotoxic chemotherapy agents act at various points throughout the cell cycle or bind to DNA, and thus have the potential to kill most cells active in the cell cycle. They cannot distinguish between a normal and neoplastic cells. Consequently, normal tissues are damaged as "innocent bystanders." Many traditional chemotherapy protocols are based on the principle of maximum tolerated dose in which the amount of chemotherapy given is dictated by acceptable toxicity to normal tissues. This remains a common approach to chemotherapy in many veterinary and human cancers. Nevertheless, the limitations of this "controlled poisoning" have impelled oncologists to find therapies that are more specifically targeted to dysregulated pathways in cancer and to view chemotherapy from other perspectives.

Metronomic Chemotherapy. This is one of the new ways of using old drugs. Metronomic chemotherapy is sometimes called low-dose, continuous chemotherapy. Rather than administering large doses of drug at relatively wide intervals (commonly every one to three weeks) as is done with conventional chemotherapy protocols, metronomic chemotherapy uses small doses of drugs given on daily to every-other-day for a prolonged period. Unlike conventional chemotherapy, in which the goal is to kill the neoplastic cells outright, the intention of metronomic chemotherapy is an antiangiogenic effect. This is achieved because the circulating endothelial precursor cells, which participate in the formation of new *continued on page 36*

Cancer *continued from page 34* blood vessels needed to nourish a tumor as it grows, are exquisitely sensitive to chemotherapy. By providing low levels of chemotherapy at frequent intervals, angiogenesis is suppressed. In laboratory animals receiving metronomic chemotherapy, production of antiangiogenic factors, such as vascular endothelial factor (VEGF) is decreased.

Metronomic chemotherapy may have additional effects. For instance, for tumors that are exquisitely sensitive to chemotherapy, metronomic dosing may provide a direct cytotoxic effect similar to fractionated radiation therapy. Moreover, there is evidence that metronomic chemotherapy may have an immune effect through suppression of regulatory T cells that allow neoplastic cells to escape immune surveillance.

Metronomic chemotherapy protocols in dogs and cats typically combine a standard dose of nonsteroidal anti-inflammatory drug with a low dose of an oral alkylating agent. Cyclophosphamide has been used most commonly in dogs, although chlorambucil and lomustine have also been incorporated into metronomic protocols. While metronomic chemotherapy is very well tolerated in most patients, monitoring for myelosuppression and gastrointestinal disturbance is needed. In human oncology, other antiangiogenic agents, such as bevacizumab (a monoclonal antibody directed against VEGF), may be incorporated into metronomic regimens.

Initial reports of metronomic chemotherapy are promising. In a small preliminary study, survival times in dogs with hemangiosarcoma treated with metronomic or conventional chemotherapy were similar. Another report indicated that the time to recurrence in dogs with incompletely resected integumentary soft tissue sarcomas was approximately doubled among dogs that received metronomic chemotherapy compared to those that received no further treatment.

The long-term consequences of metronomic chemotherapy are still unknown for this relatively new therapy. Optimal dosing and duration of therapy are still under investigation. It is also important to be mindful of appropriate patient selection for metronomic chemotherapy. Since the effects of metronomic chemotherapy may not be immediate and stabilization of disease is often considered a treatment success, patients in good clinical condition and tolerant of the current level of disease may be the best candidates for this type of therapy.

Small Molecule Inhibitors. Therapies that target dysregulated pathways in cancer have long been viewed as the ideal approach to controlling cancer while minimizing toxicity to normal tissues. The receptor tyrosine kinase (RTK) pathways are drivers of many cellular signaling pathways. Mutations in these pathways have been documented in a variety of cancers. The first small molecule inhibitor approved for humans was a RTK inhibitor, imatinib mesylate. A similar drug, toceranib phosphate (Palladia®), was the first small molecule inhibitor to receive FDA approval for dogs. The approved indication is treatment of grade II or III, recurrent cutaneous mast cell tumors. Masitinib mesylate (Kinavet®), another RTK inhibitor, recently received conditional approval.

Both toceranib and masitinib target the split-kinase family of RTKs, a member of which is Kit. Mutations in the c-kit gene have been observed in approximately 25 to 30 percent of intermediate and high-grade canine mast cell tumors. C-kit is an important regulator of mast cell growth and differentiation, and mutations in this gene have been associated with constitutive activation of the pathway. Treatment with toceranib or masitinib have been associated with regression of mast tumor or long-term stabilization of disease. Although documentation of a c-kit mutation is associated with a high biologic response rate with toceranib, about a third of dogs without the mutation have been reported to show benefit from treatment. It is speculated that the drug is working to inhibit tumor growth through other RTK pathways, such as VEGF. Indeed, recent studies indicate that toceranib may have benefit in a number of solid tumors, such as anal sac carcinoma, thyroid carcinoma, metastatic osteosarcoma, head and neck carcinoma and nasal carcinoma.

Although RTK inhibitors are not conventional chemotherapy agents, they have similar side effect profiles. Gastrointestinal side effects seem to be most common with these drugs. Monitoring of complete blood counts is also required. Other side effects have been reported. Drug holidays and/or dose reductions are often effective in managing these complications. Studies to optimizing dosing of these agents beyond the manufacturers label instructions are ongoing. Toceranib and masitinib are considered investigational in cats.

Cancer Vaccines. Therapeutic vaccines against cancer are an attractive approach to cancer treatment that have become a reality in veterinary oncology. The canine melanoma vaccine, Oncept™, was granted conditional FDA approval in 2007 and gained full licensure earlier this year. This DNA-based vaccine employs a human tyrosinase gene to stimulate an immune response against canine tyrosinase in the melanoma cells. Studies have indicated that survival in dogs with oral melanoma, one of the most aggressive tumors in dogs, was increased to approximately a year compared to approximately four months in historical controls. The recommendation for use of the vaccine is definitive local control, including aggressive surgery +/- radiation therapy, which may not have been pursued in prior patients (due to the concern about the high risk for early metastatic disease). Studies are ongoing to investigate outcomes in dogs receiving hypofractionated radiation therapy and vaccine. Nevertheless, cases of disease regression in dogs with diffuse metastatic disease have been reported.

The vaccination protocol entails four initial vaccinations two weeks apart followed by boosters every six months. The vaccine is exceptionally well tolerated. Induction of autoimmunity, a concern when the vaccine was initially introduced, has not been reported to be a problem.

Interventional Radiology. Interventional radiology entails the use of image-guided procedures, to diagnose and treat a broad spectrum of diseases, including cancer. One of the most promising procedures in veterinary oncology is chemoembolization of tumors, most commonly in the liver although other sites have been treated. This procedure typically employs fluoroscopy and angiographic techniques to identify the arterial blood supply to a tumor, after which chemotherapy is delivered directly to the tumor followed by particle embolization. The result is ischemic necrosis of the tumor as well as prevention of chemotherapy excretion from the tumor. This procedure exploits the difference in blood supply to liver tumors and normal hepatic parenchyma in that vascular supply to the tumor is largely derived from the hepatic artery while the portal system is the major supply of blood to the normal liver tissue. These

procedures are technically demanding and required experienced operators such that availability in veterinary medicine is currently limited.

Another procedure that is gaining popularity is the use of stents in veterinary cancer patients with transitional cell carcinoma. Urethral stenting is performed more commonly and can provide rapid palliation due to obstruction of urine outflow by the tumor. Ureteral stenting is also possible, but the procedure requires a greater level of expertise.

Cancer Diagnostics. Recent advances in veterinary oncology extend beyond treatment of cancers into the realm of diagnosis and monitoring. A laboratory technique that has been helpful in distinguishing reactive lymphoid proliferation from lymphoid neoplasia is the polymerase chain reaction (PCR) for antigen receptor rearrangement (PARR) test. As its name suggests, this test uses PCR testing designed to amplify the hypervariable regions of the heavy chain of the immunoglobulin receptor on B cells and the T cell receptor. Electrophoresis of the PCR products will separate according to size of the hypervariable regions in the sample. In a reactive process, the lymphocytes present would be expected to be polyclonal and the product would produce a smear or laddering effect on an electrophoresis gel. In contrast, a clonal expansion of lymphocytes would be expected to have identical hypervariable regions, producing a single band. (It should be noted that the sequence of the hypervariable region is not identified, rather identical size is used a surrogate for sequence homology.) Although this test should not be used as the sole diagnostic test for lymphoma or other lymphoid neoplasia, it has been helpful in conjunction with other tests to distinguish between neoplastic and reactive disease. An advantage of this test is that it can be run on good quality fine needle aspirate samples. False positive results can be seen with certain infectious diseases (such as Ehrlichia, Anaplasma and Bartonella). False negative results also occur. It is estimated that between 75 to 90 percent of canine lymphoma and about 65 percent of feline lymphoma cases are identified with PARR testing. Studies are underway to evaluate the utility of this test to monitor remission status in dogs and cats that have received treatment for lymphoma.

Summary. The range of options for treatment of cats and dogs is ever expanding. This is fueled by increased understanding of cancer biology and the desire of pet owners to pursue treatment in dogs and cats. The direction of new cancer therapies is toward exploiting quirks in the cancer cell biology that will target neoplastic cells yet spare normal tissues. The goal is to enhance tumor control while minimizing toxicity, thereby preserving quality of life for veterinary cancer patients and their families. ■

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to the Foundation. All donations received by Dec. 31, 2011 will be deductable to the extent allowable by law. We appreciate your thinking of us.

The PBGV board and Foundation volunteers have been a particularly great group to work with this year, and I thank them from the bottom of my heart. The Foundation board joins me in thanking all of you who have given so generously to us.

Merci!

— Lauren Kovaleff, President