

Canine Lymphoma: A New Hope!!!

Traditionally, lymphoma was lymphoma as recipe protocols were commonplace that were considered a “one size fits all” for therapy. With the advent of newer immunologic, molecular and histologic diagnostics, the treatment of lymphoma is changing. Currently, decisions regarding which chemotherapeutic agents/protocols to be utilized is now based upon tumor grade, location, histologic subtype and phenotype.

On a very basic level, lymphoma is broken down into two main phenotypes, B and T cell. Traditionally 2/3 of dogs with lymphoma are classified as B cell and 1/3 are T cell. A minor percentage (<2%) are deemed “null cell.” Phenotyping of lymphoma patients can be achieved through a variety of tests including immunohistochemistry, immunocytochemistry, PARR and flow cytometry.

- a. Immunohistochemistry (IHC): IHC is still considered the “gold standard for determining phenotype utilizing a panel of markers that bind to surface proteins either on B cells (cd79a, cd21, Pax5) or T cells (cd5, cd3, cd4, cd8). This requires tissue obtained either via a punch biopsy, tru-cut biopsy, or nodal extirpation
- b. Immunocytochemistry (ICC): ICC utilizes the same antibodies as IHC but on cytology samples thus offering a more cost effective manner to obtain phenotype. The distinction is that nodal architecture is not evaluated thus specific subtypes of lymphoma cannot be determined.
- c. Polymerase Chain Reaction (PCR): This is a repetitive enzymatic reaction that generates ~10⁹ copies of a particular DNA sequence from 1 original copy, thus a small sample can yield results. It utilizes heat-stable polymerases and sequence specific primers. This test is commonly used in the identification of infectious disease in human and veterinary medicine. PCR for antigen receptor rearrangement (PARR): Clonality is the hallmark of malignancy, and PARR amplifies the variable regions of immunoglobulin genes and T-cell receptor genes to detect the presence of a clonal population. PARR not only determines clonality (cancer) but will also determine the phenotype of lymphoma or lymphoid leukemias. Specific sites/samples that can be analyzed include: lymph node or mediastinal mass aspiration, body cavity fluids, cerebral spinal fluid, bone marrow or peripheral blood.
- d. Flow Cytometry (FCM): FCM is routinely used in human medicine early in the work-up of lymphoid malignancies and involves the use of monoclonal antibodies + fluorescent markers. This allows the evaluation of a large number of cells to determine differences in cell size (small vs large), phenotype of circulating atypical cells and presence of aberrant surface marker expression. FCM requires fresh samples of blood or tissue (lymph node, mediastinal mass) and is commercially available through major diagnostic laboratories.

T cell lymphoma is more commonly associated with certain breeds including the boxer, golden retriever, Australian shepherd, Asian lap dogs and Siberian husky. T cell LSA is also associated with certain anatomic forms including cutaneous (epitheliotropic, AKA ELSA), mediastinal, hepatic and gastrointestinal. Many studies have documented a worse prognosis for dogs with T-cell lymphoma and for this this reason, many oncologists have begun modifying protocols based upon phenotype. Further support of this was based upon a retrospective study in which the response of T cell LSA to a single dose of doxorubicin was ~50% vs ~100% for dogs with B cell LSA. The discussion was then raised to include more alkylating agents into T cell protocols based upon evidence of high responses in dogs with ELSA treated with lomustine (CCNU). Although, only 17% experienced a complete remission (CR), 61% experienced a partial remission (PR). The combination of L-asparagine, mechlorethamine, vincristine, procarbazine, and prednisone (L-MOPP) has been investigated in dogs T-cell lymphoma. Overall, L-MOPP protocol was associated with a complete remission rate of 78%, and overall survival 270 days, However, >20% were alive at >900 days. The challenge with this protocol is cost, difficulty of administration and toxicity. Currently protocols with substitutions of CCNU for doxorubicin and Elspar in each cycle are underway and are standard at this author’s practice.

Novel LSA Therapy:

Chemotherapy: Tanovea™ was discovered by Gilead Sciences, Inc., and licensed to VetDC (<http://vet-dc.com/>) for use in animal cancer, (previously known as VDC-1101) was designed to preferentially target and attack cancer cells implicated in lymphoma. In previous clinical studies, Tanovea™ has been shown to be highly effective with a 77% overall response rate. Tanovea™ was generally well-tolerated and demonstrated high rates of response in both dogs naïve to previous treatments as well as in dogs that relapsed or failed previous chemotherapy. Tanovea is administered IV on a 3 week schedule and large scale studies are underway. The goal of this study is to evaluate the effectiveness of Tanovea™ in naïve or relapse lymphoma patients. The class of drug is unlike any in our current standard chemotherapy protocols thus offers the first new LSA drug in many years and preliminary results are promising. A clinical trial evaluating Tanovea is ongoing at Hope Veterinary Specialists and Pet Emergency Services.

Monoclonal antibody therapy: A monoclonal antibody (mAb) can be used to specifically bind to target cells or proteins. This may then stimulate the patient's immune system to attack those targeted cells and remove them from the body. In human oncology, monoclonal antibodies have been developed for T and B cell Lymphoma which allows the immune system to recognize, attack and remove them. Normal lymphocytes cell can be replenished, as stem cells within the bone marrow are not targeted and as such normal cells are replenished but the cancer lymphocytes are not. These have now become standard of care therapy in human oncology. Cancer cell killing is thought to be via three mechanisms:

- Antibody-dependent cellular cytotoxicity (ADCC)
- Complement-mediated cytotoxicity (CMC)
- Induction of apoptosis (natural cell death)

Two distinctly different veterinary monoclonal antibodies are available for dogs with T cell (conditional approval by USDA; Aratana: <http://www.aratana.com/>) and B cell (full approval by USDA; Novartis/Elanco). To date they have been shown to safe and have a reasonable expectation of efficacy. Each are being evaluated in separate large scale trials (www.vetcancertrials.org) along with standard chemotherapy. If similar efficacy to their "human" counterparts is noted, they will become standard of care in veterinary medicine and further pointing toward the necessity to phenotype all LSA patients.

For a video displaying the mechanisms of action of a monoclonal antibody:
<http://aratana.com/therapeutics/pipeline/cancer>

At **Pet Emergency Services Inc.** we currently have the T cell monoclonal antibody and thus the ability to add this to our arsenal of treatments options for dogs with T cell lymphoma. This includes naïve/relapse as well as gastrointestinal, mediastinal and cutaneous lymphoma. For more information regarding the schedule of treatments. Please contact us at (717) 295-7387 for more information regarding this novel and exciting therapy.

Submitted by Dr. Craig A Clifford DVM, MS, DACVIM (Oncology)
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References

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Dr. Craig Clifford

Oncology

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Dr. Craig Clifford is our first medical oncologist at PETS and adds to our growing specialty group to provide a comprehensive team approach with internal medicine, oncology and surgery to provide new and novel therapies to the region. He is a graduate of Mississippi State University College of Veterinary Medicine and received an MS degree in Animal Science/Virology from the University of Delaware. After completing an internship and a medical oncology residency at the University of Pennsylvania, he became a diplomat of the American College of Veterinary Internal Medicine (Oncology) in 2003. Dr. Clifford is a well renowned oncologist who has authored/co-authored over 30 papers and book chapters. He was responsible for the creation of Veterinary Cancer Society resident review session and the Northeast Veterinary Co-operative Oncology Group. Dr. Clifford has served on the VCS executive board and currently on the ACVIM Exam Rating Committee, Residency Training and Credentials Committee and is the Co-chair of the Standards of Excellence in Residency Education Task Force. Dr. Clifford will also be available for CE lectures and phone consultations.

**Dr. Clifford is available every Wednesday at PETS.
Please call us at (717) 295-7387
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