Central Connection

Your Connection to Valley Central - FALL 2013

Leaders in Specialty Care

Dear Colleagues:

Welcome to our Fall 2013 newsletter. In this issue, we have included articles written by Dr. Kate Vickery, Dr. Candace Carter, and Ashley Elliot, CVT.

Our commitment is to keep you and our clients updated on medical topics and new services offered at Valley Central Veterinary Referral Center. The doctors and staff at Valley Central Veterinary Referral Center want to thank you for your sustained and continued support. Our continued goal is to provide the highest standard of veterinary care for your clients. We understand that our success as a referral hospital is a result of your confidence in the veterinary service we provide for your clients and patients. Please do not hesitate to contact any doctor or staff member with questions or concerns regarding any aspect of our veterinary hospital services.

Allyson Tolliver, Hospital Administrator

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Updates From VCVRC:

Our Surgical Department welcomes Dr. Gifford and Dr. Hayes.

We are very pleased to announce Dr. Galina Hayes and Dr. Angela Gifford have joined our Surgical Department at Valley Central Veterinary Referral Center.

Dr. Hayes is one our newest additions to our Surgical Department. She is also board certified in Small Animal Emergency and Critical Care. Dr. Hayes is originally from Manchester, England and has been a practicing veterinarian since 1998, working first in mixed practice and then in small animal general practice. She graduated from Bristol University in the UK. During her first year in practice in rural Wales, she fell in love with surgery and emergency medicine. She returned to veterinary school in Canada to complete an internship at Western Veterinary Specialist Centre. Dr. Hayes continued to complete a residency in small animal emergency and critical care medicine, and then a residency in small animal surgery. Each residency was completed at Ontario Veterinary College, University of Guelph. Along the way she completed a PhD in epidemiology and specialized in mathematical modeling of disease patterns.

She has been involved in many research projects and has published extensively both in journals and textbooks. She won the small animal resident's abstract award two years in a row at the conference of the International Veterinary Emergency and Critical Care Society.

Dr. Hayes' surgical interests include reconstructive techniques and emergency surgical procedures, however she is interested in all surgery and how it may specifically benefit the patients under her care. She is a strong proponent of evidence based medicine.

Dr. Gifford is our other newest addition to our Surgical Department. Dr. Gifford is originally from Ithaca, New York. While growing up she found veterinary medicine to be the perfect combination of her interests in dog training and biology. After completing her undergraduate

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Updates From VCVRC (continued)

degree in biology at St. Bonaventure University, Dr. Gifford, continued onto Cornell University College of Veterinary Medicine where she completed her veterinary degree in 2009. During veterinary school she participated in research on reproductive disease of the dog and the congenital disorder petcus excavatum. She was awarded the American Animal Hospital Association Student Achievement Award in Medicine and Surgery, the Neuroanatomy and Clinical Neurology Award, the Westminster Kennel Club Foundation Veterinary Scholarship, and the Finger Lakes Kennel Club Veterinary Scholarship.

Dr. Gifford completed a rotating internship in small animal medicine and surgery at Oradell Animal Hospital in New Jersey, and then moved to Rhode Island to complete a three year residency in surgery at Ocean State Veterinary Specialists. During residency, her research focused on surgical oncology and the use of chemotherapy beads in the treatment of various soft tissue tumors dogs, cats, and rabbits.

Dr. Gifford enjoys all types of surgery, including emergency, soft tissue, neurologic, oncologic, and orthopedic surgery. She has participated in several AO courses on orthopedic repair. She offers TTA, TPLO, and extracapsular stabilization for the repair of cruciate deficient stifles. Dr. Gifford has taken an interest in minimally invasive and interventional techniques. Her own cat has undergone ureteral stenting and ureteral bypass, providing a firsthand view of the advantages of these procedures. Beyond surgery, Dr. Gifford has keen interest in patient care and pain management, striving to treat the entire patient throughout their surgical treatment.

Dr. Hayes and Dr. Gifford have begun accepting new patients. Both doctors have extensive experience in arthroscopic, laparoscopic and interventional radiology procedures. Our surgical team is proud to offer the highest quality surgical services at VCVRC.

ONCOLOGY

Kate Vickery, V.M.D., M.S., D.A.C.V.I.M.

Metronomic Chemotherapy

Conventional cancer treatment utilizes chemotherapy at the maximally tolerated dose (MTD), or the highest dose shown to be both cytotoxic and tolerable for the patient. MTD chemotherapy targets rapidly dividing cells including: tumor cells and normal cells of the gastrointestinal tract and bone marrow[1]. Since MTD chemotherapy targets normal cells, a mandatory hiatus between treatments is required to allow these cells to recover and repopulate. During this recovery time, the tumor cells also have the opportunity to repopulate and acquire genetic changes which lead to drug resistance[1].

In an attempt to avoid these pitfalls of conventional chemotherapy treatment, a new method of chemotherapy administration, metronomic chemotherapy, has developed in the past few years. Much like a metronome keeps continuous rhythm; metronomic chemotherapy is the administration of chemotherapy at continuous intervals[2]. Due to higher dosing frequency, the cytotoxic agent must be administered at dosages lower than MTD to ensure tolerability and administered in a form that enables ease of use. The majority of metronomic chemotherapy protocols that have been studied in veterinary medicine use oral anti-neoplastic agents, such as cyclophosphamide, lomustine, or chlorambucil[3-6]. This new method of chemotherapy administration is still under investigation, especially with regard to optimization of the proper drugs, dose, schedule, and tumor applications.

However, the low cost, ease of administration, and acceptable toxicity profiles potentially associated with this therapeutic strategy make metronomic chemotherapy protocols attractive and suitable to veterinary patients.

The main mechanism of action of metronomic drug delivery is the inhibition of tumor angiogenesis[2-7]. The process of angiogenesis, or new blood vessel formation, is imperative for the tumor cells to grow and metastasize[7]. The metronomic strategy is based on the fact that endothelial cells are highly sensitive to continuous exposure to low doses of chemotherapeutic drugs[2-7]. There are several proposed mechanisms for the anti-angiogenic effects of metronomic chemotherapy including: targeting the drug-sensitive endothelial cells of tumors, inhibiting the mobilization of endothelial precursors from the bone marrow, and stimulating the production of thrombospondin-1, an endogenous anti-angiogenic protein[5-7]. In addition, when exposed to cytotoxic agents, endothelial cells are less likely to undergo genetic mutations that lead to drug resistance when compared to their tumor cell counterparts[7].

Metronomic chemotherapy has also been shown to exert anti-tumor immunity through inhibition of regulatory T cells (Tregs)[8]. Tregs are a subset of CD4+ lymphocytes that normally function to keep the immune system in check and prevent

Metronomic Chemotherapy (continued)

autoimmunity. Several studies have documented a high level of circulating Tregs in both human and canine cancer patients[9-10]. In these cases, Tregs prevent the patient's endogenous immune system from attacking and destroying the cancer cells. Additional studies have shown that the administration of metronomic cyclophosphamide in both human and canine cancer patients selectively decreases circulating Treg numbers, thereby promoting the host immune response to destroy tumor cells[8-10].

The majority of metronomic chemotherapy protocols incorporate anti-inflammatory drugs, specifically cyclooxygenase (COX) inhibitors. COX is a prostaglandin synthase enzyme which has been implemented in tumor cell promotion and progression[11]. One of the proposed mechanisms by which this occurs is through upregulation of angiogenesis through the production of pro-angiogenic cytokines such as vascular endothelial growth factor (VEGF), transforming growth factor beta, and endothelin – 1[11]. More recent research suggests cyclooxygenase may stimulate tumor cell production of Tregs, thereby downregulating anti-tumor immunity[12]. In veterinary patients, COX inhibitors, such as piroxicam or deracoxib, have been shown to elicit antitumor activity in patients with transitional cell carcinoma[13-14], prostatic carcinoma[15], oral squamous cell carcinoma[16], oral malignant melanoma[16], and inflammatory mammary carcinoma[17]. The potential anti-angiogenic effects of these drugs support their inclusion in metronomic protocols.

There have been several published reports evaluating metronomic protocols for spontaneously developing tumors in client-owned dogs[3-6]. One of the first reports evaluated the safety and efficacy of metronomic cyclophosphamide, etoposide, and piroxicam as adjuvant therapy for dogs with stage II splenic hemangiosarcoma[6]. A total of nine dogs were enrolled in the study. Their treatment outcomes were compared to historical controls consisting of 24 dogs with stage II splenic hemangiosarcoma treated with the standard of care chemotherapy, adjuvant doxorubicin. The study found that the treatment protocol was well tolerated by the majority of dogs and that the disease-free interval was improved in dogs receiving the metronomic protocol over the dogs receiving doxorubicin. The authors concluded that the results showed promising preliminary evidence that metronomic protocols are safe and may be effective, however the results should be interpreted with caution due to the small number of dogs included as well as the use of historical controls.

Another study evaluated metronomic cyclophosphamide and piroxicam in canine patients with incompletely excised soft tissue sarcomas[5]. Eighty-five dogs were included in the study, 55 dogs were used as contemporary controls while 30 dogs were given treatment. The majority of the patients in both arms of the study had grade 2 tumors. 40% of the treated dogs developed mild side effects including: anorexia, vomiting, increase serum creatinine concentration, and sterile hemorrhagic cystitis. The study revealed that dogs receiving treatment had a longer disease-free interval of approximately 400 days compared to dogs that received surgery alone (disease-free interval of 211 days). The authors of this study concluded that this treatment protocol was fairly well tolerated and it was effective in delaying tumor recurrence in dogs with incompletely resected soft tissue sarcomas. These results should be interpreted with caution due to the retrospective nature of the study.

A recent study evaluated the tolerability of metronomic lomustine in dogs with cancer[4]. Eight-one dogs with a variety of naturally occurring primary or metastatic tumors were given metronomic lomustine and side-effects were evaluated. The treatment was discontinued in nearly 30% of dogs due to severe toxicosis. Side-effects described include: gastrointestinal, thrombocytopenia, increased alanine transferase, neutropenia, and progressive azotemia. Nearly 10% of dogs developed some degree of azotemia during the treatment protocol. The authors concluded that metronomic lomustine was tolerated in dogs without pre-existing renal compromise but that caution should be used when administering this agent as the risk for side effects was fairly high in this study.

Another recent study evaluated the safety and efficacy of metronomic chlorambucil in dogs with cancer[3]. Thirty-six dogs with a variety of tumors were included in the study. The majority of patients tolerated the treatment well with only 11% of dogs reporting low grade gastrointestinal side effects. Complete remission was achieved, and lasted over 35 weeks in three dogs (mast cell tumor, soft tissue sarcoma and thyroid carcinoma). Partial remission was noted in 1 dog with histiocytic sarcoma (39 weeks duration). The overall remission rate for the study was 11% (4 of 36 dogs). Stable disease was noted in 17 dogs (47%) with various other cancers. The median progression-free interval was 61 days, and the median survival time was 153 days. The authors concluded that chlorambucil given in a metronomic protocol showed low toxicity profile and antitumor activity in dogs with a variety of naturally occurring cancers. The results of the study should be interpreted with caution due to variety of tumor types included and the small sample size in each tumor population.

In summary, preliminary veterinary studies[3-6] have shown promise for metronomic chemotherapy although both the human and veterinary medical community has a great deal to learn, especially with regard to optimization of the proper drugs, dose, schedule, and tumor applications. The low cost, ease of administration, and acceptable toxicity profiles make these protocols attractive and suitable to veterinary patients. These protocols, however, should be used with caution as they are still considered investigational and the studies noted above[3-6] just skim the surface on safety and efficacy. Larger, case-controlled, prospective trials are needed before these protocols become widely accepted. These protocols should not be used in place of the standard of care treatment and clients should understand the investigational nature of these protocols before initiating treatment on their pet.

Metronomic Chemotherapy (continued)

References

1. Chabner. Cancer Chemotherapy and Biotherapy. 3rd ed. 2001.
2. Buckstein, R, et al. High-dose celecoxib and metronomic 'low-dose' cyclophosphamide is an effective and safe therapy in patients with relapsed and refractory aggressive histology Non-Hodgkin's Lymphoma. *Clin Cancer Res* 2006; 12(17): 5190-5198.
3. Leach TN, et al. Prospective trial of metronomic chlorambucil chemotherapy in dogs with naturally occurring cancer. *Vet Comp Oncol*. 2012 Jun;10(2):102-12.
4. Tripp CD, et al. Tolerability of metronomic administration of lomustine in dogs with cancer. J Vet Intern Med. 2011 Mar-Apr;25(2):278-84.
5. Elmslie RE, et al. Metronomic therapy with cyclophosphamide and piroxicam effectively delays tumor recurrence in dogs with incompletely resected soft tissue sarcomas. *J Vet Intern Med*. 2008 Nov-Dec;22(6):1373-9.
6. Lana S, et al. Continuous low-dose oral chemotherapy for adjuvant therapy of splenic hemangiosarcoma dogs. *J Vet Intern Med*. 2007 Jul-Aug;21(4):764-9.
7. Kerbel RS. The anti-angiogenic basis of metronomic chemotherapy. *Nature Reviews. Cancer* 2004; 4: 423-436.
8. Burton JH, et al. Low-dose cyclophosphamide selectively decreases regulatory T cells and inhibits angiogenesis in dogs with soft tissue sarcoma. *J Vet Intern Med*. 2011 Jul-Aug;25(4):920-6.
9. Wilke CM, et al. Prognostic significance of regulatory T cells in tumors. *Int J Cancer* 2010; 127: 748-758.
10. Biller, BJ. Use of FoxP3 expression to identify regulatory T cells in healthy dogs and dogs with cancer. *Vet Immunol Immunopathol* 2007; 116: 69-78.
11. Flory, AB, et al. The role of cyclooxygenase in carcinogenesis and anticancer therapy. *Compendium for Continuing Education* Aug 2005; 616-627.
12. Baratelli, F, et al. Prostaglandin E2 induces FoxP3 gene expression and T regulatory cell function in human CD4+ T cells. *J Immunol* 2005; 175: 1483-1490.
13. Henry CJ, et al. Clinical evaluation of mitoxantrone and piroxicam in a canine model of human invasive urinary bladder carcinoma. *Clin Cancer Res*. 2003 Feb;9(2):906-11.
14. McMillan SK, et al. Antitumor effects of deracoxib treatment in 26 dogs with transitional cell carcinoma of the urinary bladder. *J Am Vet Med Assoc*. 2011 Oct 15;239(8):1084-9.
15. Sorenmo KU, et al. Evaluation of cyclooxygenase-1 and cyclooxygenase-2 expression and the effect of cyclooxygenase inhibitors in canine prostatic carcinoma. *Vet Comp Oncol*. 2004 Mar;2(1):13-23.
16. Boria PA, et al. Evaluation of cisplatin combined with piroxicam for the treatment of oral malignant melanoma and oral squamous cell carcinoma in dogs. *J Am Vet Med Assoc*. 2004 Feb 1;224(3):388-94.
17. de M Souza, et al. Inflammatory mammary carcinoma in 12 dogs: clinical features, cyclooxygenase-2 expression, and response to piroxicam treatment. *Can Vet J*. 2009 May;50(5):506-10.

INTERNAL MEDICINE

Candace Carter, D.V.M., Ph.D., D.A.C.V.I.M.

Blood Gas Analysis

Respiratory diseases can be extremely difficult to diagnose. Historically, the disease has been diagnosed by evaluating radiographs and while that can provide a lot of insight into respiratory disease, it may not provide a complete picture and does not quantitate lung function. There is also subjective component to radiographic evaluation that introduces an intangible variable of human error.

A blood gas evaluation can yield a lot of insight into respiratory function as well as acid-base status. An arterial blood sample can be attained from the femoral or dorsal pedal artery. While there is a learning curve to attaining an arterial blood gas, it only takes a little bit of practice to hone your skills and soon you will be grabbing 'arterial sticks' with ease.

The more difficult part is in interpretation and generally that just takes practice too. Let's evaluate the following case:

Scoop, a 10-year-old, M N, Pug, was presented for increased respiratory effort after having had cyberknife treatment for a pituitary tumor. Chest radiographs did reveal a moderate, diffuse bronchointerstitial lung pattern but given the breed, confirmation abnormalities and significant weight loss it was difficult to determine whether there was true consolidation of the left caudal lung lobe. Pulse oximetry showed oxygen saturation at 97% which is not markedly abnormal.

An arterial blood gas told a slightly different story.

pH 7.47 (7.36-7.44)

pCO2 23 mmHg (36-44 mmHg)

HCO3 14.8 mmol/L (24-26 mmol/L)

tCO2 14.4 mmol/L (25-27 mmolo/L)

pO2 141 mmHG (90-100 mmol/L)

Base Excess -5.8 mmol/L

Na 144 mmol/L, (144-160 mmol/L)

K 3.5 mmol/L (3.5 -5.8 mmol/L)

Cl 114 mmol/L (109-122 mmol/L)

Blood Gas Analysis (continued)

The first step is to determine whether there is a pH change. This indicates alkalosis or acidosis. In this case a high pH indicates an alkalosis. Now we need to determine whether the alkalosis is due to a metabolic problem or a respiratory problem. In this case, the body is losing CO2 an acid expired from the lungs which would cause an alkalosis. Simplistically if the pCO2 or HCO3 change is in the same direction as the pH change it is a metabolic problem, if the change is in the opposite direction, as it is in this case, than the primary cause is respiratory.

The decrease in HCO3 indicates that the kidneys are trying to compensate by excreting bicarbonate but since the pH is not normal, Scoop's body is not able to fully compensate in this way, leading to the alkalosis.

The cause of a respiratory alkalsosis is not intuitive, so I always have to review them. They include pain, hyperthermia, primary lung disease and hypoxemia. In Scoop's case we could easily rule out hyperthermia as his body temperature was normal and the blood gas proved that hypoxemia was not an issue. Pain can be more difficult to determine but since I could not localize pain on physical examination, it did seem less likely. However, the blood gas does support pneumonia, and would be a plausible explanation for the clinical signs. We did treat Scoop for pneumonia with broad spectrum antibiotics. Interestingly, we did see radiographic improvement in the appearance of the left caudal lung and his pulse oximetry improved to 99%.

In this case it was difficult to make a diagnosis of pneumonia from radiographs but the blood gas was pivotal in making a diagnosis of pneumonia in a patient with a normal pulse oximetry reading. Generally pneumonia can be easily confirmed by radiographs, pulse oximetry or by attaining a sample from a tracheal wash. In this case I was able to make a diagnosis while avoiding sedation in a potentially unstable patient thanks to the information gained by blood gas analysis.

NURSES TIP

Ashley Elliot, CVT

ACL TEARS

After an active summer at the beach, park or farm with your dog, now is the time that many animals are presenting to the veterinary clinic for a hind-limb lameness evalutaion. Hind-limb lameness in large breed dogs specifically can be the most common sign of a cranial cruciate ligament rupture (commonly known as an acl tear). Although not unheard of in small breed dogs, active large breed dogs seem to be the most common culprit (i.e. retrievers, boxers, pit bulls, and rottweilers).

Accurate diagnosis is key, as hind-limb lameness can be a symptom of several orthopedic issues. First, confirm the limp with the client, as many clients either think the limp is the opposite leg or label the leg by looking at their dog from the front. Observe the dog's gait to confirm it is in fact lame. The next step is radiographs. If an acl tear is suspected, x-ray the effected stifle(s) and also a VD pelvis including the stifles. This allows for you to view the big picture. Although you can't diagnose an acl tear from x-rays alone, it is a valuable diagnostic tool. Differentials such as fractures, osteoarthritis, luxating patellas, hip dysplasia, and bone tumors can be ruled out. You can also find chronic changes as a result of an acl tear, such as changes to the patella itself and arthritis. Finally, palpation of the entire limb is the most valuable diagnostic step, as you feel for cranial drawer and look for tibial thrust, but also rule out pain in other joints. Be sure to also evaluate the opposite limb as many of these dogs have partial or even complete tears in the opposite limb.

Once an acl tear is confirmed, you're ready for suregry for a lateral suture, TTA or TPLO. All of our surgical cases require a complete cbc and chemistry within 30 days prior to surgery. For an acl, we also require a minimum of a lateral x-ray of the effected stifle and a VD pelvis taken recently as well. If your clinic has digital x-ray, please remember to send the client with the x-rays on disk, as emailed x-rays don't always print well and always have to be repeated.

VALLEY CENTRAL
VETERINARY REFERRAL CENTER

VCVRC has been serving the Lehigh Valley and surrounding areas since 1996. We are dedicated to providing state-of-the-art veterinary care for your patients.

Specialists at Valley Central Veterinary Referral Center

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Carlos Hodges, D.V.M., M.S., P.C.
Practice limited to Surgery
Galina Hayes, B.V.S.c., Ph.D., D.A.C.V.E.C.C.
Practice limited to Surgery
Angela Gifford, D.V.M.
Practice limited to Surgery

NUCLEAR MEDICINE

Ronald Hodges, D.V.M., P.C., D.A.C.V.I.M.

INTERNAL MEDICINE

Ronald Hodges, D.V.M., P.C., D.A.C.V.I.M.
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Mary Landis, V.M.D., M.A.
Practice limited to Ophthalmology

Continuing Education Schedule

Monthly Case Conferences:
The last Thursday of the Month from 12 PM–1 PM. For your convenience we are continuing to offer monthly case meetings thru web conferencing. For more details please call the office.

Discussions about clinical cases with medicine and surgical implications.

Lunch will be provided, courtesy of Hills, by Dr. Heather Berst.

Until our new web-site is launched, please refer to our Facebook page for updates to our CE schedule. You may also email Dr. Carlos at Carlos@vcvrc.com with any questions about upcoming lectures.

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