TOP 10 Recent Advances in Veterinary Oncology

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This discussion will review what I feel to be the top 10 clinically relevant advances in veterinary oncology over the last ~ 10 years. Topic #10 will be a “stinker topic” and will briefly summarize advances that have really NOT been advances. I will post the abstracts from these publications and then summarize them in the lecture. It is important to point out that major advances in surgical and radiation oncology have occurred over the last 30 years (e.g. hemipelvectomy, limb-sparing, nasal planectomy, scapulectomy, etc.) but they will not be discussed here.

1. Six month chemo for lymphoma.  
   The purpose of this study was to compare a maintenance-free chemotherapy protocol based on CHOP (H from hydroxydaunorubicin = doxorubicin, O from Oncovin = vincristine) to a similar protocol with a maintenance phase for the treatment of canine lymphoma. Fifty-three dogs with multicentric lymphoma were treated with a 6-month modified version of the University of Wisconsin (UW)-Madison chemotherapy protocol (UW-25). Disease-free interval (DFI) and survival were compared to a historical control group of 55 dogs treated with a similar protocol with a prolonged maintenance phase. Remission rate for the study dogs was 94.2% (complete remission = 92.3%, partial remission = 1.9%). DFI and survival between the 2 groups did not differ significantly, with median DFI and survival of the study dogs equal to 282 and 397 days compared to 220 and 303 days for the control dogs (P = .2835 and .3365, respectively). Univariate analysis identified substage b (P = .0087), German Shepherd breed (P = .0199), and body weight > 18 kg (P = .0016) as significant for worse survival. Longer survival was associated with thrombocytopenia (P = .0436). Multivariate analysis revealed that substage (P = .0388) and weight (P = .0125) retained significance for DFI, whereas substage (P = .0093), thrombocytopenia (P = .0150), and weight (P = .0050) retained significance for survival. Overall, the protocol was well tolerated by the dogs, with 41.5% (22/53) requiring a treatment delay or dose modification, but only 9.4% (5/53) needing hospitalization. The 6-month chemotherapy protocol based on CHOP with no maintenance phase provides similar DFI and survival times when compared to a similar protocol with a prolonged maintenance phase.

2. FNA of non-palpable LN’s.  
   OBJECTIVE: To determine sensitivity and specificity of physical examination, fine-needle aspiration, and needle core biopsy of the regional lymph nodes for evidence of metastasis in dogs and cats with solid tumors. DESIGN: Case series. ANIMALS: 37 dogs and 7 cats. PROCEDURE: Regional lymph nodes were evaluated by means of physical examination (palpation), fine-needle aspiration, and needle core biopsy. Results were compared with results of histologic examination of the entire lymph node, the current standard. RESULTS: Tumors included 18 sarcomas, 16 carcinomas, 7 mast cell tumors, and 3 other tumors. Carcinomas were more likely to have metastasized to the regional lymph node (7/16 animals) than were sarcomas (2/18). Sensitivity and specificity of physical examination were 60 and 72%, respectively. Sensitivity and specificity of cytologic examination of fine-needle aspirates were 100 and 96%, respectively. Sensitivity and specificity of histologic examination of needle core biopsy specimens were 64 and 96%, respectively. CONCLUSIONS AND CLINICAL RELEVANCE: Results suggested that fine-needle aspiration may be a sensitive and specific method of evaluating the regional lymph nodes in dogs and cats with solid tumors, because results correlated well with results of histologic examination of the entire lymph node.
Physical examination alone was not a reliable method and should not be used to decide whether to aspirate or biopsy the regional lymph nodes.

3. Use of CT for delineation of metastases.
   A. Imaging studies in people indicate that x-ray computed tomography (CT) is a more sensitive technique than thoracic radiography for the detection of pulmonary metastatic neoplasia. Systematic studies comparing CT and thoracic radiographic techniques in veterinary patients have not been performed. The present retrospective study was designed to directly compare the efficacy of these 2 techniques in detecting pulmonary nodules in dogs. Eighteen dogs with histologically confirmed pulmonary metastatic neoplasia had contemporaneous thoracic radiographs and pulmonary CT scans compared. Quantitative analyses included estimation of pulmonary nodule size, number, and lobar distribution on thoracic radiographs and CT images. Only 9% of CT-detected pulmonary nodules were identified on thoracic radiographs (P < .003). The lower size threshold was approximately 1 mm to detect pulmonary nodules on CT images and 7-9 mm to reliably detect nodules on radiographs (P < .0001). Additionally, pulmonary nodules were detected in a significantly greater number of lung lobes using CT as compared with thoracic radiographs (P < .0001). These data indicate that CT is significantly more sensitive than thoracic radiography for detecting soft-tissue nodules in dogs. As such, thoracic CT should be considered in any patient with neoplasia that has potential for pulmonary metastasis to more reliably stage the disease, particularly when accurate characterization of the extent and distribution of pulmonary metastatic disease affects therapeutic planning.

   B. OBJECTIVE: To compare results of computed tomography (CT) and radiography with histopathologic findings in tracheobronchial lymph nodes (TBLNs) in dogs with primary lung tumors. DESIGN: Retrospective case series. ANIMALS: 14 client-owned dogs. PROCEDURES: Criteria for inclusion were diagnosis of primary lung tumor, use of thoracic radiography and CT, and histologic confirmation of TBLN status. Medical records were reviewed for signalment; history; and physical examination, clinicopathologic, radiographic, CT, surgical, and histopathologic findings. RESULTS: Tracheobronchial lymphadenopathy was not identified via radiography in any dogs. Tracheobronchial lymphadenopathy was diagnosed in 5 dogs via CT. Six dogs had histologic confirmation of metastasis to TBLNs. Radiographic diagnosis yielded 6 false-negative and no false-positive results for tracheobronchial lymphadenopathy. Computed tomography yielded 1 false-negative and no false-positive results. Sensitivity of CT for correctly assessing TBLN status was 83%, and specificity was 100%. Positive predictive value was 100%, and negative predictive value was 89%. Dogs with lymphadenopathy via CT, histologic confirmation of TBLN metastasis, or primary tumors with a histologic grade > 1 had significantly shorter survival times than their counterparts. CONCLUSIONS AND CLINICAL RELEVANCE: Results of CT evaluation of TBLN status were in agreement with histopathologic findings and more accurate than use of thoracic radiography for evaluating TBLNs in dogs with primary lung tumors. Computed tomography imaging should be considered as part of the staging process to more accurately assess the TBLNs in dogs with primary lung tumors.

   A. Chemotherapy-induced nausea and vomiting (CINV) is a common side-effect of cisplatin therapy. Maropitant (Cerenia TM ), a novel neurokinin-1 receptor antagonist, was evaluated for prevention and treatment of cisplatin-induced emesis in tumour-bearing dogs. Dogs (n = 122) were randomly allocated to three treatment groups: T01, placebo before and after cisplatin; T02, placebo before and maropitant after cisplatin; or T03, maropitant before and placebo after cisplatin. Maropitant treatment (T02) following a cisplatin-induced-emetic event resulted in significantly fewer subsequent emetic events ( P = 0.0005) than in placebo-treated dogs (T01). In placebo-treated (T01) dogs, 56.4% were withdrawn from the study because of treatment failure compared with 5.3% in group T02. When maropitant was administered prior to cisplatin treatment (T03) in a prevention regime, 94.9% did not
vomit compared with only 4.9% of placebo-treated dogs, and significantly fewer emetic events (P < 0.0001) were observed in those dogs that did vomit. In summary, maropitant was safe and highly effective in reducing or completely preventing cisplatin-induced emesis.\(^5\)

B. Maropitant (Cerenia), a selective neurokinin(1) receptor antagonist, was evaluated for safety and efficacy in treatment and prevention of acute vomiting due to various etiologies in dogs in a randomized clinical trial. Two-hundred seventy-eight dogs were enrolled from 29 veterinary hospitals. Two-hundred fifty-two were evaluable for efficacy, while 275 were evaluable for safety. A randomized block design was utilized (three maropitant- and one placebo-treated dog per block). Initial treatment was maropitant at 1 mg/kg body weight (0.45 mg/lb) or an equivalent volume of saline (placebo) administered subcutaneously. On the subsequent 1 to 4 days, maropitant or placebo (dependent on allocation) was administered subcutaneously or orally at approximate 24-h intervals as needed. Oral doses were administered as maropitant tablets using unit dosing to deliver a minimum dose of 2 mg/kg body weight (0.9 mg/lb) or equivalent numbers of similar placebo tablets. Dogs and housing were observed twice daily for evidence of vomiting. Emesis was significantly (P < or= 0.0012) reduced in maropitant-treated dogs as 50% (32/64) of placebo-treated dogs continued to vomit compared to only 21.8% (41/188) of maropitant-treated dogs. Post-treatment clinical signs were consistent with clinical diagnoses and judged not to be treatment related. In this clinical trial, maropitant was safe and effective in reducing emesis due to various etiologies in dogs.\(^6,7\)

5. Palladia.\(^8\)

A. The purpose of this study was to determine the objective response rate (ORR) following treatment of canine mast cell tumors (MCT) with toceranib phosphate (Palladia, SU11654), a kinase inhibitor with both antitumor and antiangiogenic activity through inhibition of KIT, vascular endothelial growth factor receptor 2, and PDGFRbeta. Secondary objectives were to determine biological response rate, time to tumor progression, duration of objective response, health-related quality of life, and safety of Palladia. EXPERIMENTAL DESIGN: Dogs were randomized to receive oral Palladia 3.25 mg/kg or placebo every other day for 6 weeks in the blinded phase. Thereafter, eligible dogs received open-label Palladia. RESULTS: The blinded phase ORR in Palladia-treated dogs (n = 86) was 37.2% (7 complete response, 25 partial response) versus 7.9% (5 partial response) in placebo-treated dogs (n = 63; P = 0.0004). Of 58 dogs that received Palladia following placebo-escape, 41.4% (8 complete response, 16 partial response) experienced objective response. The ORR for all 145 dogs receiving Palladia was 42.8% (21 complete response, 41 partial response); among the 62 responders, the median duration of objective response and time to tumor progression was 12.0 weeks and 18.1 weeks, respectively. Palladia-treated responders scored higher on health-related quality of life versus Palladia-treated nonresponders (P = 0.030). There was no significant difference in the number of dogs with grade 3/4 (of 4) adverse events; adverse events were generally manageable with dose modification and/or supportive care. CONCLUSIONS: Palladia has biological activity against canine MCTs and can be administered on a continuous schedule without need for routine planned treatment breaks. This clinical trial further shows that spontaneous tumors in dogs are good models to evaluate therapeutic index of targeted therapeutics in a clinical setting.

6. Melanoma Vaccine.\(^9,13\)

A. Canine malignant melanoma (CMM) is an aggressive neoplasm treated with surgery and/or fractionated RT; however, metastatic disease is common and chemoresistant. Preclinical and clinical studies by our laboratory and others have shown that xenogeneic DNA vaccination with tyrosinase family members can produce immune responses resulting in tumor rejection or protection and prolongation of survival. These studies provided the impetus for development of a xenogeneic DNA vaccine program in CMM. MATERIALS AND METHODS: Cohorts of three dogs each received increasing doses of xenogeneic plasmid DNA encoding either human tyrosinase (huTyr; 100/500/1500
mcg), murine GP75 (muGP75; 100/500/1500 mcg), murine tyrosinase (muTyr; 5 dogs each at 100/500 mcg), muTyr+/−HuGM-CSF (9 dogs at 50 mcg muTyr, 3 dogs each at 100/400/800 mcg HuGM-CSF, or 3 dogs each at 50 mcg muTyr with 100/400/800 mcg HuGM-CSF), or 50 mcg MuTyr intramuscularly biweekly for a total of four vaccinations. RESULTS: The Kaplan-Meier median survival time (KM MST) for all stage II-IV dogs treated with huTyr, muGP75 and muTyr are 389, 153 and 224 days, respectively. Preliminarily, the KM MST for stage II-IV dogs treated with 50 mcg MuTyr, 100/400/800 mcg HuGM-CSF or combination MuTyr/HuGM-CSF are 242, 148 and >402 (median not reached) days, respectively. Thirty-three stage II-III dogs with loco-regionally controlled CMM across the xenogeneic vaccine studies have a KM MST of 569 days. Minimal to mild pain was noted on vaccination and one dog experienced vitiligo. We have recently investigated antigen specific antibody and T-cell responses in dogs vaccinated with HuTyr. CONCLUSIONS: The results of these trials demonstrate that xenogeneic DNA vaccination in CMM: (1) is safe, (2) leads to the development of anti-tyrosinase antibodies, (3) is potentially therapeutic, and (4) is an attractive candidate for further evaluation in an adjuvant, minimal residual disease Phase II setting for CMM.

7. **Diagnostic Imaging Advances.** To be reviewed at the lecture with special emphasis on importance to feline vaccine-associated sarcoma.

8. **Do we really need Elspar for Lymphoma??**

   A. The purpose of this study was to evaluate response rates, 1st remission duration (FRD), and toxicity in dogs with previously untreated lymphoma receiving an identical CHOP-based combination chemotherapy protocol with or without L-asparaginase (LASP). One hundred fifteen dogs with lymphoma were scheduled to receive an identical CHOP-based chemotherapy protocol that included L-ASP. However, because of manufacturer-imposed random rationing, 31 dogs did not receive L-ASP as scheduled. The 2 treatment groups were statistically similar with respect to signalment and presence of historical negative prognostic factors. No difference was observed in the median FRD whether dogs did or did not receive L-ASP (206 versus 217 days, respectively; \( P = .67 \)). No difference was observed in the median overall survival times between dogs receiving or not receiving L-ASP (310 versus 308 days, respectively; \( P = .84 \)). No statistical difference was observed with respect to overall response rate between dogs that did or did not receive L-ASP (89.3% versus 87.1%, respectively; \( P = .75 \)). Complete response rates between the groups also were no different (83.3% and 77.4% for L-ASP and non-L-ASP groups, respectively; \( P = .59 \)). Prevalence of toxicity (neutropenia, diarrhea, or vomiting) and treatment delays (\( P = .80 \)) also were similar between groups. The results of this study suggest that exclusion of L-ASP in this multidrug protocol does not significantly impact outcome. Therefore, it may be more appropriate to reserve the use of L-ASP for treating relapse in dogs with lymphoma that have failed induction therapy.\(^{14}\)

   B. Combination chemotherapy is superior to single-agent chemotherapy for treating canine lymphoma, but the effect of each drug on efficacy remains unknown. By comparing 34 dogs treated with a modified cyclophosphamide, vincristine, prednisone (COP) chemotherapy protocol and 42 dogs given asparaginase in the induction phase of the same protocol, the effect of asparaginase on the chemotherapeutic protocol was determined. Both groups were compared based on clinical response at 2 weeks and 6 weeks, and on the progression-free interval. Asparaginase did not significantly increase the likelihood of a clinical remission or prolong the initial progression-free interval in the dogs studied.\(^{15}\)

9. **Zinecard for the attenuation of side effects from adriamycin/doxorubicin extravasation.** To be reviewed at the lecture with special emphasis on practical use of this extremely new medication.\(^{16}\)

10. **Putting the cart before the horse.** To be reviewed at the lecture with special emphasis on MAb 231, Acemannan, Bladder TCC tests, Gemzar and others.
References

9. Bergman PJ, Camps-Palau MA, McKnight JA et al. (), Development of a xenogeneic DNA vaccine program for canine malignant melanoma at the Animal Medical Center, *Vaccine* 2006;24: 4582-4585