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## ADVANCES IN HEMANGIOSARCOMA TREATMENT

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### Introduction

Hemangiosarcoma (HSA) is a tumor with which most veterinary practitioners are well familiar. For most dogs, the diagnosis of HSA is a harbinger of bad things to come; most veterinarians consider this tumor to be the 'kiss of death'. Improvements in diagnosis and therapy of HSA have been slowly emerging, and new

therapeutic opportunities are on the horizon. All HSA are highly malignant neoplasms. Most primary HSA lesions arise in the spleen, liver, right atrium or subcutaneous tissues. Approximately 25% of cases have concurrent right atrial and splenic involvement at the time of diagnosis. Regardless of the site of origin, local infiltration and systemic metastases are the common growth patterns. Some investigators have suggested that the skin and subcutaneous sites are less aggressive but metastatic behavior from these locations has been observed. True intradermal HSA can arise in non-pigmented, non-haired skin of dogs and cats as a result of chronic ultraviolet light exposure; these lesions may behave in a more benign manner.

Hematogenous metastatic spread occurs as an early event in the natural history of HSA. Metastatic sites are widespread, with the lung and liver being the most frequently affected organs. Many other tissues are sites of HSA metastases including kidney, adrenal glands, lymph nodes, muscle, brain, mesentery, and skin. Regardless of location, morbidity and mortality is often due to acute internal hemorrhage secondary to tumor rupture. Dogs require stabilization and acute emergency management at the outset when the disease is diagnosed. Diagnostic evaluation consists of abdominal ultrasound or radiographs, 3 view thoracic radiographs for metastatic disease, potentially echocardiography to evaluate for an atrial mass, and a CBC, serum chemistry profile, and coagulation studies. A study published in 2004 from Ohio State suggested that contrast-enhanced CT scanning of the spleen may be valuable in differentiating benign from malignant lesions. Because between 25-50% of dogs presenting for splenic lesions ultimately are found to have benign disease rather than hemangiosarcoma, it is important to establish the diagnosis through biopsy. We perform fine needle aspiration cytology of splenic and liver lesions under ultrasound guidance, after warning clients that these assays may necessitate moving the schedule of surgery up if acute bleeding is

induced. Hemangiosarcoma cells are often anaplastic on cytology and resemble high-grade spindle cell tumors, with occasional epithelioid differentiation as well. Immunohistochemically, these lesions should be positive for vascular endothelial markers such as Factor VIII-related antigen and CD31. Experimentally, HSA cells are also positive for CD117 (c-Kit), the hematogenous stem cell factor receptor, CD105 (endoglin surface marker) and alpha(v)beta(3) integrin, which is a marker of neoangiogenic blood vessels.

HSA should be considered a systemic disease requiring a multimodality approach to therapy. After definitive treatment of the primary tumor, rigorous long term follow-up consisting of hematologic, radiographic, and ultrasonographic studies is required. Repeat radiographs and ultrasound exams are conducted every 6 to 8 weeks. Once diagnosed, dogs should be treated with adjuvant chemotherapy, optimally combined with some form of inhibitor of angiogenesis.

### Radiation therapy consideration

The role of radiation therapy for curative treatment of hemangiosarcoma in dogs is limited. Although irradiation may be beneficial for achieving local tumor control, it is difficult to justify putting a patient through extensive treatment when metastatic disease is imminent. However, there may be a role for radiation in the palliation of bulky, non-resectable subcutaneous hemangiosarcoma lesions. The goal of palliative radiation therapy is to relieve pain or improve function and or quality of life in patients with systemic disease, and to cause minimal treatment related effects. In a study of 20 dogs treated at Colorado State University, 14 of 20 dogs treated with palliative radiation had subjective reduction in tumor size, with 4 dogs achieving a complete response. Median survival duration was 95 days (range 6 to 500 days). The radiation was administered in 6-8 Gy fractions and patients received 1-4 fractions. Because this was a retrospective study, more definitive conclusions about the value of radiation therapy for hemangiosarcoma are difficult to draw.

### Chemotherapy and medical management considerations

The initial treatment for dogs with HSA is most often surgical excision of the primary lesion. Many dogs will be presented in hypovolemic shock because of acute hemorrhage and will require an immediate whole blood transfusion. This will provide needed RBCs, platelets,



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and coagulation factors. Most emergency/critical care specialists have an opinion of the best treatment protocol for managing DIC; however, there is no general consensus among these specialists. Because of cardiac hypoxia, some dogs will have premature ventricular contractions, increasing their surgical risk. Arrhythmias should be managed appropriately, and surgical resection of the splenic tumor will often result in transient, self-limiting arrhythmias.

Most dogs with completely resected HSA do not experience long-term survival, due to development of metastatic disease that is not amenable to surgical removal. Median survival times for dogs following splenectomy have ranged from 56 to 70 days. However, small numbers of dogs have survived more than one year following splenectomy alone for HSA. Dogs treated for right atrial HSA by surgical excision had a reported survival of 90 to 150 days. Only small numbers of patients have tumors suitable for this type of surgery, and the post-operative morbidity and prolonged recovery period after thoracotomy in the face of inevitable and widespread metastasis makes this therapeutic recommendation questionable for most dogs. We are currently following a cohort of dogs at MSU that had right atrial appendage amputation followed by chemotherapy. The study is ongoing, but we currently have 2 dogs alive 6 months after surgery.

The use of chemotherapy following excision of HSA appears to provide the longest survival times. Doxorubicin is the most effective single agent in the treatment of HSA. A study from Penn evaluated 20 dogs treated with a dose intensified doxorubicin protocol for canine HSA. These dogs received 30 mg/M<sup>2</sup> doxorubicin at 2 week intervals for 5 treatments. Results were median survival times of 257, 210, and 107 days respectively for Stage I, II, and III disease. This is not appreciably different from other reported studies.

### **VAC protocol**

The most efficacious protocols include doxorubicin and cyclophosphamide with or without vincristine (VAC protocol). The median survival time of 18 dogs treated with VAC, in combination with surgery, was 190 days with 30% surviving at least one year. The VAC protocol has been modified to include several variations at individual cancer centers. The VAC protocol currently in use at MSU is as follows:

- Day 1: Doxorubicin 30 mg/m<sup>2</sup> IV and cyclophosphamide 100-150 mg/m<sup>2</sup> IV or 50 mg/m<sup>2</sup> PO on days 3, 4, 5, and 6 of week 1 only
- Day 8, 15: Vincristine 0.75 mg/m<sup>2</sup> IV (at MSU we routinely lower the dose to 0.5 mg/m<sup>2</sup> IV on days 8 and 15 to reduce the incidence of myelosuppression and GI signs)

The cycle is repeated on day 22. Four to six cycles are

administered. Myelosuppression is appreciable for many dogs, and it may be necessary to use the lower dose of cyclophosphamide. If the neutrophil count is less than 1500/μl on day 8, the treatment is postponed for one week. Antibiotics can be administered orally from day 1 to 14 to minimize systemic bacterial infections. Approximately 25% of VAC-treated dogs show GI toxicity and some will require hospital attention.

### **DAV protocol**

A protocol involving doxorubicin and dacarbazine, with or without vincristine, may also be useful for treatment of HSA in dogs. We are currently evaluating DAV as an open pilot study of dogs with both measurable non-resectable HSA and as an adjuvant treatment. We are accruing a cohort of approximately 25 dogs to assess response, toxicity, and survival duration. We have seen responses to this protocol in the face of bulky non-resectable subcutaneous, hepatic, and pulmonary metastatic disease, which allowed us to move the protocol forward into an adjuvant disease setting. Data are maturing, but the protocol shows promise as an adjunctive and salvage protocol. The DAV protocol for soft tissue sarcomas is administered at 21-day intervals for 4-6 total cycles. The protocol is as follows:

- Day 1: Doxorubicin 30 mg/m<sup>2</sup> IV and Dacarbazine 800 mg/m<sup>2</sup> IV as an 8-hour infusion
- Day 8, 15: Vincristine 0.5 mg/m<sup>2</sup> IV

This is an aggressive and myelosuppressive protocol that requires careful monitoring to manage leukopenia and the potential for sepsis. For dogs less than approximately 0.75 m<sup>2</sup>, it may be necessary to perform dose reduction on the first cycle of therapy, and attempt escalation to full dose therapy on successive cycles if the protocol is tolerated by the patient. Gastrointestinal toxicity in the form of vomiting while receiving the infusion necessitates the addition of metoclopramide injection at the end of the infusion period. We generally prescribe metoclopramide orally for 3 days on a PRN basis after the 8-hour DTIC infusion. Recently, the antiemetic maropitant has also proven useful in managing toxicity of this protocol. The oral formulation of dacarbazine, is also being used in a dose of 100 mg/m<sup>2</sup> PO daily for 5 days in this protocol. Emesis is a problem, and we are currently accruing cases to determine efficacy.

### **Immunotherapy and novel therapy approaches**

Currently, surgery followed by adjuvant chemotherapy, usually using a doxorubicin containing protocol is the standard of care for this tumor. Despite these treatments, dogs still die early from metastases. Use of immunomodulatory drugs, such as interferon-α 2a (Roferon®) combined with the chemotherapeutic regimen postoperatively has been attempted in an investigational pilot study.



There is much enthusiasm for antiangiogenic therapies that are looming on the horizon. Canine hemangiosarcoma is an ideal tumor for these agents because it arises from a transformed endothelial cell. Drugs such as the monoclonal antibody bevacizumab, and small molecular vascular endothelial growth factor inhibitors such as gefitinib and sunitinib may prove useful for veterinary patients, but much study is required to validate the dose, efficacy, and safety of these approaches.