

Canine Hemangiosarcoma: Rational Future Targets

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Hemangiosarcoma (HSA) is a malignant neoplasm which originates from vascular endothelium and accounts for 0.3-2% of all canine cancers. Large breed dogs such as German Shepherd Dogs, Golden Retrievers, and Labrador Retrievers are over represented with a median age at diagnosis of 9-10 years. Most frequently affected primary sites of HSA in these patients include the spleen, skin, and heart (right atrium and auricle). Other less common sites include the liver, lungs, kidney, muscle, oral cavity, bone, and the urinary bladder. Clinical signs can be nonspecific or consist of acute weakness or collapse with corresponding abdominal distension, tachycardia, tachypnea, pale mucus membranes, and weak pulses. These clinical signs are often secondary to acute blood loss into the peritoneal or pericardial cavity.

Standard of care treatment for HSA depends primarily on tumor location but in large part consists of surgery followed by chemotherapy. The chemotherapeutic agent of choice for HSA is Doxorubicin. For strictly dermal HSA, chemotherapy is not necessary following complete surgical removal with adequate margins. However, for the remaining HSA locations surgery alone affords the patient with a median survival time of less than 2 months. Even with the addition of chemotherapy, the majority of patients will succumb to their disease within 4-8 months. Death is usually secondary to metastatic disease via hematogenous spread to the pulmonary parenchyma and intraabdominal dissemination primarily, but also to the skin, bones, and brain.

Pathology and natural behavior

Malignant endothelium serves as the underlying pathology of HSA, and hence HSA can involve any organ requiring nutrition and oxygen via blood circulation. Often dogs presenting for visceral organ HSA will present with signs associated with acute tumor rupture and resultant hemorrhage and hypovolemic shock. Symptomology reflects the hemodynamic instability of these acutely bleeding patients and include lethargy, weakness, collapse, anorexia, mucous membrane pallor, delayed capillary refill time, tachycardia, tachypnea, cardiac arrhythmias, and poor pulse quality. In circumstances where the patient does not experience a life-threatening hemorrhage event, clinical symptoms might recur and take on an episodic pattern. With primary splenic or hepatic HSA, tumor rupture results in abdominal distention and a noticeable fluid wave secondary to hemorrhagic effusion. With primary cardiac HSA, muffled heart sounds, venous congestion, and signs compatible with cardiac tamponade may be noted. Primary subcutaneous and intramuscular HSA, typically occur as large, firm or fluctuant masses. Overlying skin may be ecchymotic and ulcerated.

Diagnosis and staging

Presumptive diagnosis of HSA can be made based upon multiple clinical and physical findings, as well as patient signalment. However, baseline diagnostics which should be considered in any patient with presumed HSA might include the following:

- Complete blood count
 - Anemia: secondary to hemorrhage
 - Schistocytes: red blood cell morphology
 - Thrombocytopenia: immune mediated destruction, splenic sequestration, severe hemorrhage, and/or disseminated intravascular coagulopathy (DIC)
 - Neutrophilic leukocytosis
- Serum chemistry panel
 - Hypoproteinemia: secondary to blood loss
 - Liver enzyme elevations: involvement of hepatic parenchyma
 - Hypoglycemia: rare paraneoplastic syndrome
- Coagulation panel
 - Elevations in clotting times: disseminated intravascular coagulation
 - Defects in both primary and secondary coagulation cascades
- Thoracic radiography
 - Evaluation of overt lung metastases
 - Cardiac involvement with globoid cardiac silhouette
 - Pericardial effusion
- Echocardiography
 - Evaluation of right auricle or atrial mass effects
 - ECG might demonstrate ventricular arrhythmias and electrical alternans
- Abdominal ultrasound

- Evaluate primary abdominal tumor involvement, as well as regional metastases within the visceral organs residing within the peritoneal cavity
- Cytology
 - Considered insensitive for diagnosis given poorly exfoliative nature of sarcomas
- Biopsy
 - Required for definitive diagnosis
 - Diagnostic and therapeutic

Canine hemangiosarcoma treatment options

Due to the devastating prognosis for HSA, multiple new therapies outside the realm of surgery and standard doxorubicin administration have been devised and evaluated. These include various alternative chemotherapeutic protocols, intracavitary chemotherapy administration, immune modulation, matrix metalloproteinase inhibitors, antiangiogenic therapy, and tumor vaccines.

Combination chemotherapy protocols with doxorubicin, cyclophosphamide and vincristine (VAC) or doxorubicin and cyclophosphamide (AC) have been evaluated. Unfortunately, the addition of these chemotherapeutic agents to standard treatment with doxorubicin afforded no significant increase in survival times with median survival times of 172 and 179 days respectively. A dose intensified doxorubicin protocol has also been evaluated with doxorubicin being administered every 2 weeks instead of every 3 weeks, however median survival time was not statistically different from that of standard treatment methods. Intraperitoneal administration of liposome encapsulated doxorubicin has been evaluated as the abdomen is a main site of progression of disease and thus it is logical to treat them with a drug that due to its liposome encapsulation and pegylated nature should have a longer half-life in the plasma. Unfortunately, again survival times did not vary significantly from those previously reported.

Tumors require angiogenesis for growth and thus anti-angiogenic drugs have been and are currently being heavily investigated for the use in a multitude of tumors. Minocycline, an antiangiogenic metalloproteinase agent with anticollagenase activity, was evaluated in combination with doxorubicin and cyclophosphamide for treatment of dogs with hemangiosarcoma. Regrettably, the addition of this drug revealed no significant survival advantage with an all too familiar median survival time of 170 days. Additionally continuous low dose chemotherapy with the combination of etoposide, cyclophosphamide, and piroxicam was evaluated in 9 dogs diagnosed with stage II splenic HSA. The goal of this study was to see if this combination of drugs, which targets the tumor neovasculature itself, would improve survival times in contrast to traditional therapy. Survival times of the dogs in this study were comparable to other previously established studies and known survival times.

Immune modulation via administration of a liposome-encapsulated muramyl tripeptide-phosphatidylethanolamine (L-MTP-PE), a synthetic derivative of a component of bacterial cell walls, in combination with chemotherapy afforded the longest survival times of all above novel treatment options. L-MTP-PE activates macrophages and monocytes leading to increased tumoricidal activity. While the survival time of dogs treated with this therapy (277 days) is the longest seen in the literature, there were an equivalent number of dogs with stage I as compared with stage II and this likely biased the results. Further study with a larger sample size of stage II HSA would be interesting but, studies have not been pursued further due to the lack of availability of this product to the veterinary community at this time, due to high cost and limited supply.

As immune modulation seems to be one of limited treatment options which may improve overall survival times in dogs with hemangiosarcoma, a vaccine prepared from lysates of allogenic canine HSA cell lines was evaluated in 28 dogs. Vaccines were given intraperitoneally once per week for 5 weeks then once monthly for three additional treatments. The vaccine was often given in combination with standard doxorubicin doses. Of the 6 dogs evaluated for antibody production, all 6 mounted a strong response to the vaccine and side effects were minimal. No statistically significant improvement in survival time was seen.