Review

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Treatment of Canine Hemangiosarcoma: 2000 and Beyond

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Canine hemangiosarcoma (HSA) is an aggressive and malignant neoplasia with a grave prognosis. Surgery and chemotherapy have limited success in prolonging survival times and increasing quality of life in dogs with HSA. Advances in medical oncology are resulting in increased survival rates and a better quality of life for veterinary cancer patients. An understanding of mechanisms of metastasis has led to the development of new treatments designed to delay or inhibit tumor spread. Promising new treatment options include novel delivery systems (inhalation or intracavitary chemotherapy); use of immunomodulators such as liposome-encapsulated muramyl tripeptide-phosphatidylethanolamine; antimetastatic agents such as inhibitors of angiogenesis (interferons, thalidomide), matrix metalloproteinase inhibitors, and minocycline; dietary modifications; and gene therapy. Inhibitors of angiogenesis seem to be safe and, unlike conventional chemotherapy, do not induce drug resistance. Although many of the newer approaches are still under development and review, the use of multimodality therapy incorporating innovative treatment modalities may offer the best therapeutic option for dogs affected with HSA.

Key words: Angiogenesis inhibitors; Interferon; Matrix metalloproteinase inhibitors; Minocycline; Muramyl tripeptide-phosphatidylethanolamine; Thalidomide.

Hemangiosarcoma (HSA) is a highly malignant tumor of endothelial cells that occurs more frequently in dogs than any other domestic species and is characterized by a high case fatality rate.[1–4] The overall prevalence is reported to be 0.3–2.0% of all tumors in dogs.[1,2] The mean age of affected dogs at the time of diagnosis is 9–12 years.[1–4] HSA affects almost every dog breed; however, German Shepherd Dogs, Golden Retrievers, Labrador Retrievers, and Schnauzers are predisposed.[1–4] No sex predilection has been proven, although many reports have shown an increased prevalence in males.[1–4] The etiology of HSA is unknown, although the strong breed association suggests an inherited or familial predisposition. In humans, exposure to thorium dioxide or arsenical or vinyl chloride compounds has been linked to the development of HSA.[5] Cutaneous HSA is generally found in lightly pigmented dogs, suggesting a possible correlation with ultraviolet light exposure.[6] Another hypothesized contributory factor to HSA formation in dogs is local irradiation.[7].

HSA has the potential to affect any tissue in the body, with the 3 common primary sites being the spleen (28–50%), right atrium and auricle (3–50%), and skin or subcutaneous tissue (13%).[1,8–10] Other primary sites include liver, kidney, bladder, prostate, peritoneum, lung, pulmonary artery, aorta, muscle, bone, oral cavity, tongue, vertebral body, and central nervous system.[2,10–17] Metastasis and local infiltration occur early in disease. The liver, omentum, and lung are the most common sites of metastasis.[1–4] Metastasis may occur hematogenously or via local seeding after tumor rupture. Up to 25% of splenic tumors have a corresponding cardiac tumor (right atrial and auricular).[1,2] Initially, the cardiac tumor was thought to be metastatic; however, these now generally are accepted to be 2 separate primary tumors.[12] Cutaneous HSA tends to have a lower metastatic rate, and apparently the deeper the tumor, the greater the likelihood of metastasis. In dogs with advanced HSA, determining the primary site often is not possible.

The goals of this article are 3-fold: 1st, to provide a brief historical overview of treatment options for HSA; 2nd, to examine more recent treatment options; and 3rd, to offer a glimpse into several current projects that may hold promise for the future treatment of HSA.

Traditional Therapy

Historically, surgery has been the treatment of choice for HSA, although it does little to improve overall survival times.[4,18,19] Three studies of dogs with splenic HSA treated by surgery alone reported median survival times of 2–3 months.[4,18,19] Surgical excision for cardiac HSA also yields unsatisfactory results, with median survival times ranging from 3 to 5 months.[20–22] Cutaneous HSA is generally associated with longer survival times.[23] Because of the limitations of surgery, chemotherapy has evolved into a principal component of therapy.[11] Various protocols based on doxorubicin with and without the addition of vincristine and cyclophosphamide have been reported to have the best survival times.[2,3,24–27] Published protocols include single-agent doxorubicin (30 mg/m^2 intravenously every 3 weeks for up to 5 cycles); doxorubicin and cyclophosphamide (doxorubicin as for single-agent protocol, with cyclophosphamide incorporated at 50–75 mg/m^2 intravenously on days 3–6 of every 3-week cycle); and vincristine, doxorubicin, and cyclophosphamide (doxorubicin as for single-agent protocol, with cyclophosphamide incorporated at 100 mg/m^2 intravenously on day 1 of every 3-week cycle, and vincristine at 0.75 mg/m^2 intravenously on days 8 and 15 of each cycle).[1–3,24–26] Survival times ranging from 140 to 202 days have been reported for the various doxorubicin-based protocols, although no protocol is clearly superior.[3,24–27] Iden-

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tification of additional or alternative therapeutic modalities that will prolong survival time in dogs with HSA clearly is needed.

Novel Delivery Systems

An understanding of the metastatic behavior of HSA has prompted the design of protocols tailored to the prevention of metastases. Many dogs with HSA die of pulmonary and intra-abdominal metastatic disease. Additional locally delivered chemotherapy aimed at common metastatic sites may have the potential to retard metastasis and prolong survival.[28]

Inhalation chemotherapy is 1 strategy aimed at inhibiting pulmonary micrometastasis. Efficacy and safety studies with inhalation chemotherapy have been performed in several dogs with splenic HSA.[28] After splenectomy, dogs received 4 cycles of doxorubicin and cyclophosphamide every 3 weeks in conjunction with inhaled doxorubicin. The inhaled doxorubicin was a newly developed formulation that was administered via a specially designed aerosol device. Radiographs and abdominal ultrasound were performed after the completion of the 4th cycle and every 2 months thereafter. Interim analysis of data suggests that this protocol may be efficacious and no increase in toxicity due to concurrent systemic doxorubicin chemotherapy has been noted.[28]

Sterically stabilized liposomes are liposomes containing a small fraction of membrane glycolipid or other surface stabilizer that acts as a stearic barrier outer membrane.[29] This formulation results in decreased uptake by the monocytic phagocytic system thereby prolonging tumor exposure to the drug.[29] Pegylated liposomal-encapsulated doxorubicin[a] is a unique doxorubicin delivery system.[29] Doxil has been evaluated in dogs with a variety of malignancies, including HSA, and has enhanced tumoricidal effects, decreased cardiotoxicity, and sustained drug blood levels compared to doxorubicin.[29,30]

The abdominal cavity is another common site of metastatic tumor spread in HSA patients.[31] One approach to abdominal metastases is the intracavitary administration of chemotherapeutic agents such as cisplatin or carboplatin. The use of intracavitary cisplatin has been described in dogs with various intra-abdominal tumors.[32] The efficacy of intra-abdominal carboplatin in dogs with overt abdominal metastatic HSA is being investigated (Post, personal communication). However, because carboplatin has less tissue diffusion and penetration ability than cisplatin, carboplatin is unlikely to have improved efficacy against HSA.[33,34]

Immunomodulators

Biologic response modifiers used in combination with chemotherapy are efficacious in the treatment of canine HSA.[35,36] Muramyl tripeptide-phosphatidylethanolamine (MTP-PE) is a lipophilic derivative of muramyl dipeptide (MDP), a synthetic molecule that resembles a fragment of the peptidoglycan cell wall of various bacteria. Both MDP and MTP-PE can nonselectively activate cells of macrophage lineage into a tumorcidal state, and both can be encapsulated in liposomes for optimal drug delivery.

Liposome-encapsulated MTP-PE (L-MTP-PE), when given with chemotherapy, increases disease-free interval and survival time in canine osteosarcoma patients.[35] L-MTP-PE has also been evaluated in conjunction with chemotherapy in dogs with HSA.[35] In 1 study of 32 dogs with splenic HSA, splenectomized patients were divided into 2 treatment groups.[35] One group was administered doxorubicin and cyclophosphamide (AC) at 3-week intervals for 4 treatments as well as L-MTP-PE twice weekly for 8 weeks. The control group received AC and placebo (empty liposomes). The median survival time for the AC and L-MTP-PE combination group was 277 days, which was significantly better than for the group receiving only AC (143 days). Survival times using AC and L-MTP-PE in combination also compared favorably to previously reported survival times with protocols such as vincristine, doxorubicin, and cyclophosphamide (187 days) or AC (178 days).[24,25] Little additional research with L-MTP-PE in dogs affected with HSA has been published. The lack of ongoing research interest in L-MTP-PE may be due to the limited supply of the specific liposome system for veterinary use and the high cost of the product. Newer and more cost-effective liposomal delivery systems may become available within the next few years.

Antimetastatic Agents

The metastatic ''cascade'' is a step-wise process by which neoplastic cells grow and spread to other locations in the body (Fig 1). Briefly, the stages of the cascade include transformation, angiogenesis, motility and invasion, embolism and entrance into circulation, lodgment in capillary beds, adherence to capillary walls, extravasation into organ parenchyma, adjustment to local microenvironment, tumor cell proliferation, and then further angiogenesis. An understanding of the processes involved in metastasis allows for the production and use of agents designed to control specific steps within the metastatic cascade.

The following section will discuss several agents capable of altering metastasis through effects on angiogenesis (interferon, thalidomide), prevention of matrix breakdown (matrix metalloproteinase inhibitors, minocycline), and dietary modifications. Many of the agents discussed below have either been or are in the process of being examined for treatment of canine HSA.

Inhibition of Angiogenesis

Angiogenesis is the formation of new vessels from existing microvessels. This is an essential component of metastasis, providing the principal route by which tumor cells leave the primary tumor site and enter the circulation.[37] Tumors are hypothesized to exist for an indefinite period of time without neovascularization until cells within the tumor ''switch'' to an angiogenic phenotype.[38] Tumors can induce angiogenesis by altering the local environment via overexpression of angiogenic factors, recruitment of local cells and induction of their release of angiogenic factors, mobilization of angiogenic proteins from the extracellular matrix, or reduction of the release of antiangiogenic tissue factors.[38] Conversely, tumors may also inhibit angiogenesis by activating angiogenic inhibitors that can modulate new vessel formation both at the primary tumor and at meta-

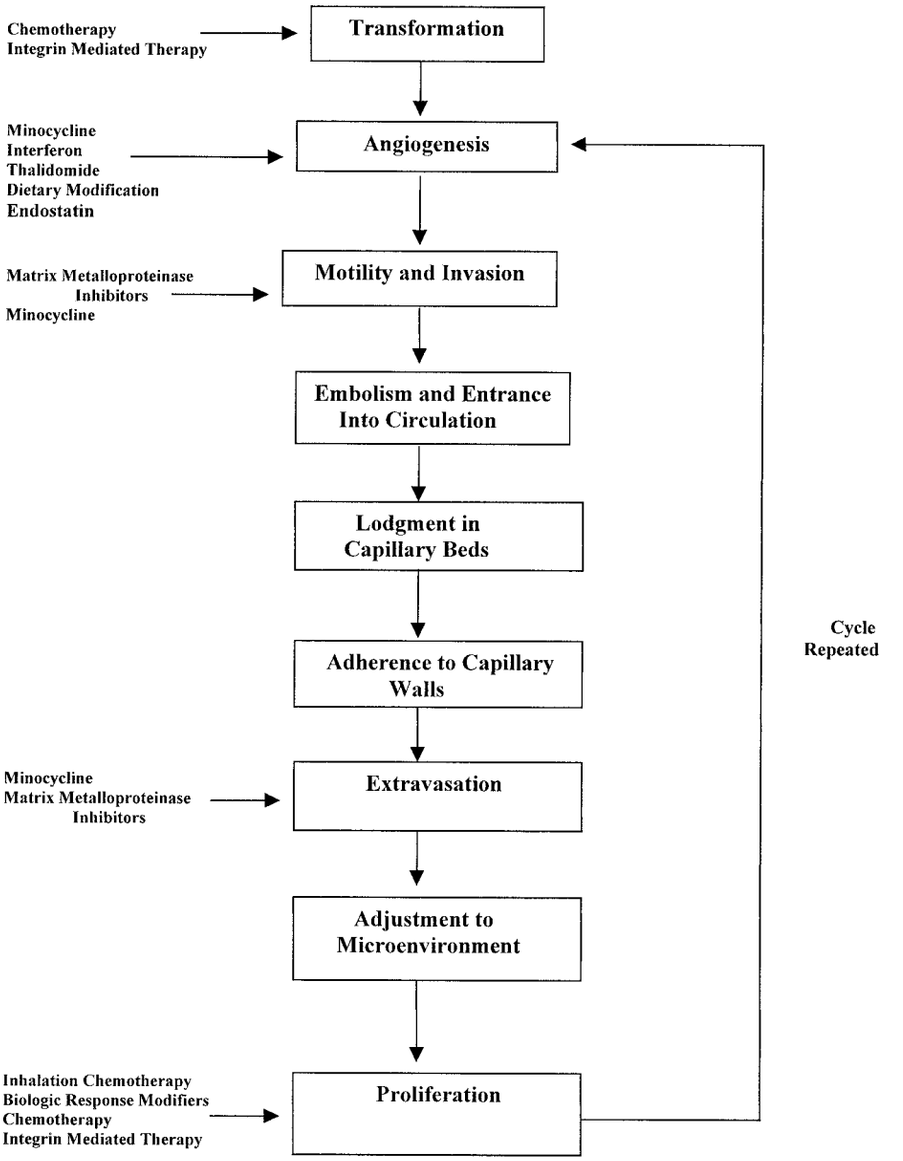

Fig 1. The stages involved within the metastatic cascade. Listed to the left are agents specifically directed against each corresponding stage.

static sites. Loss of angiogenic inhibitors may explain the proliferation of lung metastasis sometimes seen after removal of the primary tumor observed in dogs with osteosarcoma and HSA.

At least 15 proteins are known to activate endothelial cell growth and movement, including fibroblastic growth factor, vascular endothelial growth factor, angiogenin, transforming growth factors, tumor necrosis factor alpha, epidermal growth factor, platelet-derived endothelial cell growth factor, placental growth factor, interleukin-8, granulocyte-stimulating factor, and proliferin.[38] Vascular endothelial growth factor and basic fibroblastic growth factor are expressed by many tumors and act directly on endothelial cells, whereas transforming growth factor and platelet-derived growth factor attract and activate inflammatory cells or connective tissue cells, which in turn control angiogenesis.

In general, the 4 primary strategies used to design antiangiogenic agents are blockade of the factors that stimulate the formation of new vessels, utilization of natural inhibitors of angiogenesis, blockade of the molecules that allow newly formed vessels to invade surrounding tissue, and incapacitation of newly dividing endothelial cells. Some of the known inhibitors of angiogenesis include angiostatin, endostatin, angiostatic steroids, interferons, interleukin-12, retinoic acid, and tissue inhibitor of matrix metalloproteinase-1 and -2.[38–40] Angiogenesis inhibitors do not produce adverse effects such as the bone marrow suppression and gastrointestinal symptoms commonly associated with chemotherapeutic agents and do not seem to induce multidrug resistance.[41] Approximately 20 angiogenesis inhibitors are currently being evaluated in phase I or phase II human clinical trials and 3 have entered phase III trials.[38,39,42]

Interferons. The interferons (alpha and beta) are among the most well-recognized angiogenic inhibitors in human medicine and are efficacious in the treatment of children with hemangiomas.[43–46] Interferon treatment can induce complete regression of hemangiomas previously unresponsive to other therapies.[47] Interferon alpha-2a seems to inhibit angiogenesis via suppression of basic fibroblastic growth factor and vascular endothelial growth factor production. Basic fibroblastic growth factor is one of the proteins overexpressed by hemangiomas in children, whereas vascular endothelial growth factor serum levels are elevated in humans with another vascular neoplasm, angiosarcoma.[38,48] Urine concentrations of basic fibroblastic growth factor are increased in dogs with transitional cell carcinoma but have yet to be reported in dogs with HSA.[49]

Interferon alpha is commercially available and has entered phase III clinical trials for a variety of human malignancies.[39,42] Several current clinical studies veterinary studies are underway evaluating interferon alpha-2b in combination with standard chemotherapy (AC, doxorubicin) as well as with another antiangiogenic agent, thalidomide (Vail and Post, personal communication). The major potential disadvantages of interferon use in dogs are expense and poor owner compliance with daily injections. Neutralizing antibodies may eventually be produced against the interferon, thereby limiting efficacy and necessitating the use of higher doses; however, this is yet to be proven. In human medicine debate is ongoing as to whether or not anti-interferon antibodies have a significant impact on the efficacy of interferon therapy.[50,51]

Thalidomide. Thalidomide, a noted teratogenic drug, is an inhibitor of angiogenesis.[52] Thalidomide likely inhibits vascular endothelial growth factor, basic fibroblastic growth factor, and tumor necrosis factor alpha, and may offer an attractive alternative in cancer treatment because of its ability to inhibit angiogenesis and prevent tumor necrosis factor alpha–associated cachexia.[52–54] Inhibition of tumor necrosis factor alpha seems to be dose dependent, and high doses of thalidomide may be necessary to achieve a therapeutic effect.[52] One potential advantage of thalidomide is the paucity of adverse effects associated with its usage in nonpregnant dogs.[55] Thalidomide has entered phase II human clinical trials for the treatment of a variety of malignancies.[39,54,56–58] Thalidomide is currently being examined in a phase I and phase II veterinary clinical study as a single agent in dogs with a variety of malignancies and thus far the drug seems to be well tolerated.[55] Thalidomide is also currently being evaluated in several clinical veterinary trials in dogs with HSA alone or in combination with a standard chemotherapy, doxorubicin (Khanna, Post, Matthews, and Meleo, personal communication).

One potential disadvantage of thalidomide and of any inhibitor of angiogenesis is that obvious beneficial effects may be slow to develop. Because inhibitors of angiogenesis in theory will only impair new vessel development, such drugs may have little or no effect on pre-existing tumor tissue. Therefore, although inhibitors of angiogenesis may prevent tumor metastases, additional therapeutic modalities are needed to reduce the size of the pre-existing tumor burden.

Matrix Metalloproteinase Inhibitors

The matrix metalloproteinases are a family of at least 26 membrane-bound or secreted zinc-endopeptidases.[41,59–64] These enzymes can degrade many components of the extracellular matrix, including fibrillar and nonfibrillar collagens, fibronectin, laminin, and basement membrane glycoproteins.[39,59,63–65] The matrix metalloproteinases play an important role in normal physiologic conditions such as wound healing, pregnancy, and other processes involving tissue remodeling.[59,60,65] Tissue inhibitors of matrix metalloproteinases also exist that maintain a balance between extracellular matrix destruction and formation. In the healthy animal, a delicate balance exists between cell division, matrix formation, and matrix degradation.

The extracellular matrix constitutes a major barrier to tumor growth and metastatic ability.[66] Malignant tumors can sometimes utilize matrix metalloproteinases to overcome this extracellular barrier.[59,66] Matrix metalloproteinases are implicated not only in the promotion of tumor invasion of blood or lymphatic vessels but also in the regulation of proliferation at primary and secondary sites and the production and maintenance of a local environment that will enable tumor growth.[60,63,65,66] Increased matrix metalloproteinase activity has been documented in human cancer patients and has been associated with poor survivability in some patients.[59,60,63,66] Dogs with neoplasia reportedly have increased matrix metalloproteinase activity compared to normal dogs.[62]

Most matrix metalloproteinases are synthesized by stromal cells rather than by neoplastic cells, suggesting an interaction between neoplastic cells and cells within the immediate environment.[59,66] Matrix metalloproteinase receptors are present on stromal cells and must also be present on tumor cells in order for binding and activation of matrix metalloproteinases to occur.[59,66] In cancer states, an imbalance may exist between matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases. Naturally occurring tissue inhibitors of matrix metalloproteinases have inhibited tumor-induced angiogenesis in experimental systems.[59,64] Because of their short biologic half-life in vivo, naturally occurring tissue inhibitors of matrix metalloproteinases are not suitable for clinical studies. Therefore, synthetic matrix metalloproteinase inhibitors with pharmacologically enhanced activity have been developed; examples include Marimastat, Bay 12–9566, AG3340, CGS27023A, COL-3, and BMS-275291.[40] In experimental studies, matrix metalloproteinase inhibitors have reduced primary tumor growth rates, localized spread, and distant metastasis.[63] Additive effects were observed when these agents were used in combination with cytotoxic drugs. Several synthetic matrix metalloproteinase inhibitors have entered phase III human clinical trials for treatment of lung, breast, ovarian, pancreatic, and prostate cancers.[63–67]

In veterinary medicine the relationship between matrix metalloproteinases and neoplasia is not completely understood. Research is centered on identifying matrix metalloproteinases and determining associations with various malignancies.[62,65,68–71] The clinical application of such studies will hopefully lead to the design of specific matrix metalloproteinase inhibitors for adjuvant treatment. Preliminary

investigation of matrix metalloproteinase inhibitors for the treatment of a variety of malignant neoplasms is underway (Ogilvie, personal communication).

Tetracycline Derivatives

Minocycline, a semisynthetic derivative of tetracycline that has both antiangiogenic and matrix metalloproteinase inhibitory properties, has become the focus of several human cancer studies. Minocycline seems to inhibit local collagenase activity, thereby preventing angiogenesis. Whether this mechanism is due to inhibition of matrix metalloproteinases or via a matrix metalloproteinase–independent mechanism is unknown.[72] Minocycline has been efficacious in studies involving intracranial glioma in human patients and islet cell carcinoma and Lewis lung carcinoma in laboratory animals.[73–75] One study in which dogs with HSA received either chemotherapy (AC protocol) alone or chemotherapy and minocycline did not demonstrate a significant difference in survival times.[76] However, minocycline may provide benefit in dogs with less advanced disease.[76]

Dietary Modifications

Recently, a great deal of attention has been directed toward nutritional aspects of the veterinary cancer patient.[77–84] Numerous metabolic abnormalities have been associated with neoplasia. The paraneoplastic syndrome used to describe these abnormalities is cancer cachexia, which is characterized by weight loss despite adequate nutritional intake. Carbohydrate, lipid, and protein metabolism are all adversely affected in cancer patients.

The clinical impact of cancer-associated metabolic abnormalities has led to the use of dietary manipulation in an attempt to lessen cancer cachexia. A diet low in simple carbohydrates with a moderate amount of a highly bioavailable protein source supplemented with omega-3 fatty acids and specific amino acids such as arginine, glycine, glutamine, and cysteine may be beneficial to some cancer patients.[77] One of the key components to the dietary management of cancer is the utilization of a fat source as the major dietary energy component, with attention to the type and ratio of fatty acids with the diet.[77,84] High-fat diets may have 2 major beneficial effects in cancer patients.[77,78,80,84] First, tumors seem to be inefficient in using fat as an energy source, and a diet that is high in fat-derived calories may effectively ''starve'' neoplastic cells compared to normal body cells.[77,80,84] Second, omega-3 fatty acids in particular have been shown to possess antiangiogenic properties, and inhibit tumor development in animal models.[78] Eicosapentaenoic acid, an omega-3 fatty acid, has tumorcidal effects without damaging normal cells in experimental tumor models.[78] A recent double-blind, randomized study evaluated the effect of a specialized diet high in polyunsaturated omega-3 fatty acids and arginine on metabolic parameters, chemical indices of inflammation, quality of life, and disease-free interval and survival time of dogs with lymphoma.[77] Decreased levels of lactic acid were noted in patients on the special diet and these dogs had significantly longer disease-free interval and survival times compared to control animals.[79] A comparable commercial diet has since been developed that is designed to enhance survival time and quality of life in canine cancer patients (Hill's Neoplasia Diet [ND]).[b] Although the ND diet was designed for dogs with lymphoma, its use in other neoplasia seems plausible.[85] Because animals with HSA have been shown to develop cancer cachexia, it stands to reason that dietary therapy may be a viable modality of treatment. Currently, a veterinary study is examining the effect of dietary manipulations on dogs with HSA (Ogilvie, personal communication).

Beyond 2000

Other exciting and promising potential therapies for canine HSA include the use of antibodies directed against specific antigens or receptors on tumor cell surfaces and the development of recombinant angiogenic inhibitors. Integrins are adhesion molecules that mediate cell-matrix and cell-cell interactions.[86,87] They are important in several biological events including cell differentiation, malignant transformation, immune functions, and coagulation.[86,87] Integrins are expressed on the surface of many cells including osteoblasts and endothelial cells.[86,87] Integrins have been identified in dogs with osteosarcoma, and research is underway to determine integrin expression levels in dogs with HSA.[87] The integrin families may serve as an attractive target for antibodies, chemotherapeutic agents, or cell growth inhibitors.

Another plausible avenue is the use of recombinant angiogenic inhibitors as a method to prevent metastasis and tumor growth. Currently, a canine recombinant endostatin, a natural angiogenic inhibitor, is being developed and may be used in clinical trials in the near future (Khanna, personal communication).

Conclusion

HSA is an aggressive and malignant neoplasia, and affected dogs have a grave prognosis. Surgery and chemotherapy have had limited success in prolonging survival times and increasing quality of life in canine HSA patients. However, recent advances in care and treatment are increasing survival times and providing a better quality of life for affected dogs. With the development of new screening methods, early detection of HSA may allow treatment to commence before the development of overt clinical signs or grossly detectable disease.[76] The identification of new molecular mechanisms involved in the metastatic cascade has opened the doors for the development of unique treatments designed to utilize various biologic avenues. In particular, inhibition of angiogenesis has been the focus of numerous clinical studies. Inhibition of angiogenesis seems to be safe and, unlike chemotherapy, does not induce drug resistance. Although many of the agents discussed are still undergoing development and review, the use of a multimodality approach incorporating innovative treatment modalities apparently may offer the best therapeutic option for dogs affected with HSA.

Footnotes

[a] Doxil, Sequus Pharmaceuticals Inc, Menlo Park, CA
[b] Hill's Neoplasia Diet, Hill's Pet Nutrition, Topeka, KS

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