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OSTEOSARCOMA IN DOGS

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CLINICAL PRESENTATION

Appendicular OSA is generally a disease of middle aged to older, large or giant breed dogs. There is a slight peak in age incidence reported for dogs from 18 to 24 months of age; thus, some consider this disease to have a bimodal age distribution. One third of all appendicular OSA affects dogs weighing >40 kg, whereas smaller dogs are more likely to develop axial OSA. Breeds reported to be at higher risk for appendicular OSA include Great Danes, Saint Bernards, Irish Setters, Doberman pinschers, German shepherds, and golden retrievers. Recent reports indicate a likely predisposition in greyhounds and Rottweilers, as well. The two most common sites are the distal radius and proximal humerus. Common rear limb sites include the distal femur and tibia, as well as the proximal tibia. The predilection for forelimb sites may relate to the fact that more weight is borne by the forelimbs, although this etiologic link has not been convincingly demonstrated. Because OSA lesions most commonly affect the metaphyseal region of long bones, epiphyseal or diaphyseal lesions should raise an index of suspicion for alternative diagnoses. Common OSA sites in the axial skeleton, in descending order of incidence, include the mandible, maxilla, spine, cranium, ribs, nasal cavity and paranasal sinuses, and pelvis. Extrasketal sites including the eyes, liver, kidney, spleen, adrenals, subcutis, mammary tissue, testicles, vagina, and gastric ligament are uncommonly affected.

DIAGNOSIS AND STAGING

When a dog of typical signalment presents with acute lameness and limb swelling, and no known history of trauma prior to presentation, primary bone neoplasia should be considered a top differential. Radiographic imaging is often the first logical step in arriving at a diagnosis. Varying degrees of osteolysis and a proliferative response typical of osteoblastic activity are common radiographic findings. Two classic radiographic appearances described in the literature regarding OSA include 1) the "sunburst appearance" of periosteal proliferation radiating from the cortical axis and 2) "Codman's triangle", which is a triangular shaped proliferation of new bone that may be seen over the cortex at the periphery of the tumour. Although neither of these radiographic signs is pathognomonic for OSA, both can support a presumptive diagnosis. Other bone cancers, both primary and metastatic, can mimic the radiographic appearance of primary OSA, as can osteomyelitis and some benign bone lesions. Signs that support alternative diagnoses include lesions that cross the joint (typical of synovial cell sarcoma, but not OSA), diaphyseal tumour location (more common with metastatic lesions), and "punched out" areas of lysis (typical of multiple myeloma). Bone biopsy provides diagnostic confirmation, but is only indicated when it will change the treatment plan. The procedure carries with it some risk of bone fracture, given the weakened character of the diseased bone, so it is imperative to use careful technique that is likely to yield a diagnostic sample. Whereas veterinarians are generally trained to obtain biopsy samples from the border of normal and abnormal tissues, bone biopsy specimens should be obtained from the centre of the lesion. This is because biopsy tissue obtained from the periphery of an OSA lesion may yield a diagnosis of

reactive bone. Bone biopsy specimens obtained via a Jamshidi instrument have a reported accuracy rate of 91.9% for differentiation of neoplastic from non-neoplastic bone disorders, and 82.3% for distinguishing tumour type. Fine needle aspiration is a technique that was once dismissed as a low-yield procedure for bone tumours, but is now gaining popularity. In a letter published in *The Veterinary Record*, Loukopoulos, et al, noted that in 70% of canine OSA cases for which cytology and histopathology results were examined, cytology alone was sufficient to differentiate malignant from non-malignant lesions, which is often the clinically relevant question for which tumour sampling is performed. The advent of immunocytochemistry to detect alkaline phosphatase in cytology samples has improved the diagnostic accuracy of this method greatly and may obviate the need for more invasive diagnostic techniques.

Tumour staging is crucial to developing a sound treatment plan for dogs with bone cancer. Approximately 90% of dogs with appendicular OSA are thought to have micrometastatic disease at the time of diagnosis and 10 to 15% may have lesions in other bones. Accordingly, 3-view thoracic radiographs, a complete orthopaedic examination to assess for other limb involvement, and long bone radiographs or bone scan to assess for bone metastases or concurrent orthopaedic diseases are warranted. Although practitioners routinely image the thorax for staging purposes, it is the author's experience that they are less likely to recommend bone survey radiographs or nuclear scintigraphy as part of the initial diagnostic workup. However, it has been reported that there is a greater likelihood of detecting other primary or metastatic lesions on bone survey radiographs than on thoracic films. The cost differential between survey radiographs and a nuclear bone scan is negligible at many facilities. In the author's opinion, a bone scan is warranted when surgical intervention is being considered because scintigraphy can detect early metastatic or concurrent primary bone lesions that may become problematic if an amputation is pursued. Other pre-treatment tests should include a complete physical exam with particular attention to orthopaedic, cardiac and neurological evaluation, a complete blood count to assess for underlying infectious disease and to determine if surgery and chemotherapy are feasible, and serum biochemical and urine analysis. Serum biochemical evaluation may help determine which treatment options are appropriate (or inappropriate, as would be the case for cisplatin in a dog with renal insufficiency) and may provide an indication of prognosis. Several reports have shown that high levels of serum alkaline phosphatase prior to treatment warrant a poor prognosis for dogs with appendicular OSA.

TREATMENT OPTIONS

Therapy selection should be tailored to each individual patient and should take into consideration the patient's weight, orthopaedic and neurological status, degree of lameness and cortical bone destruction, tumour site, and concurrent medical problems. In addition, the client's goals and financial limitations must be considered. The two primary goals of therapy for OSA are: (1) pain relief and (2) control or slowing of metastatic disease. In general, a combined modality approach is necessary to achieve both goals. A summary of indications, contraindications, and anticipated outcome for some current OSA treatment options is provided below.

Amputation Alone

Limb amputation is likely to provide rapid pain relief, provided the patient is orthopaedically and neurologically stable and has no other concurrent bone lesions. Unfortunately, without adjuvant therapy to address micrometastatic disease, amputation is only a palliative procedure. The one-year survival rate with amputation alone is less than 10% and the mean survival time is four to five months.

Amputation and Chemotherapy

A combination of amputation and chemotherapy is the current standard of care for dogs with OSA. In addition to the previously mentioned contraindications for limb amputation, the toxicity of each chemotherapy agent must be considered in light of the dog's organ function and cardiovascular health. Likewise, the method of drug delivery for each chemotherapy agent is relevant to individualized protocol design. For example, cisplatin requires substantial fluid diuresis that may be poorly tolerated by patients with compromised cardiac or respiratory function. Doxorubicin is a severe vesicant and, as such, may not be the best choice for fractious patients or those likely to move during infusion unless sedation or venous access port placement are options. Cost is another practical consideration when choosing chemotherapy protocols. In the US, the drug cost of carboplatin is now comparable to the cost of treating with cisplatin, whereas doxorubicin is considerably less expensive than both platinum drugs. Reported survival times for amputation and chemotherapy are summarized below. DFI = median disease free interval; MST = median survival time; NR = not reported:

Protocol	1-yr survival	DFI (days)	MST (days)	Reference
Cisplatin single agent	38 to 62%	165-226	262-413	Kraegel, et al; Straw, et al; Berg, et al
Carboplatin single agent	35.4%	123 - 257	207 – 321	Bergman, et al; Vail, et al.
Combination Doxorubicin/Cisplatin	NR to 48%	NR to 470	300-540	Mauldin, et al; Chun, et al; Berg, et al
Single agent Doxorubicin	50.5%	NR	366	Berg, et al
Carboplatin (175 mg/m ²) and Doxorubicin (15 mg/m ²) over 2 days for 4 treatments	NR	195	235	Bailey, et al.
Alternating Carboplatin and Doxorubicin x 3 each	48%	227	320	Kent, et al.
Loboplatin 35 mg/m ² x 4	31.8%	NR	NR	Kirpensteijn, et al.

Other medical therapy

Medical therapy focused on pain management and addressing complications associated with pathologic bone resorption have gained attention in the past decade. Bisphosphonates have been evaluated for safety and efficacy in reducing bone pain associated with primary or secondary bone cancer. In a report by Fan et al, pamidronate administered at a mean dosage of 1 mg/kg IV q28d was clinically safe and provided subjective improvement in pain control in 4 of 10 treated dogs. Other methods of pain control include nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and drugs effective against neuropathic pain, including gabapentin.

Limb-sparing Surgery

Limb-sparing surgery may be a reasonable option for dogs that are poor candidates for amputation, provided the clients fully understand the potential benefits and complications. While limb function is improved in the majority of dogs after limb-spare, complications such as osteomyelitis occur in roughly 1/3 of all dogs undergoing the procedure. Recent data suggest that for dogs receiving adjuvant carboplatin, limb-spare provides longer MST than amputation. Factors that may contribute to this finding include infection of surgical sites in limb-spare patients which could lead to enhanced immune response, patient selection bias by tumour site, size, and severity, and occult factors such as use of certain antibiotics and NSAIDs that could affect tumour growth and angiogenesis. Dogs undergoing limb-spare surgery fare better in terms of overall survival if their surgical site becomes infected. Oncologists at Colorado State University have reported a MST of 480 days for limb-spare/chemotherapy treated dogs with infected limb-spare sites, compared to 228 days for dogs without infected sites.

External Beam Radiation

Radiation therapy can provide pain palliation for dogs with OSA. For this indication, radiation is typically delivered on a Day 0-7-21 or a Day 0-7-14-21 schedule on an outpatient basis. Clinical response rates (as determined by pain palliation) have exceeded 70%, with responses generally lasting for 2 to 2.5 months. Techniques to deliver intra-operative radiation to the primary site of OSA are also under investigation, as are stereotactic radiosurgery techniques. It is hoped that these methods will provide a more effective means of utilizing radiation for local control, not just palliation, of OSA.

Bone-targeting Radioisotopes

The bone-targeting radiopharmaceutical agent, $^{153}\text{Sm-EDTMP}$ (Quadramet™) has shown promise for treatment of primary bone tumours in dogs and other species and is FDA-approved for treatment of bone metastases in people. It is available for clinical use only at institutions licensed to handle the level of radioactivity associated with the radioisotope, but has been utilized for canine applications in the US, South Africa, Australia, and Italy. Our experience with $^{153}\text{Sm-EDTMP}$ at the UMC indicates that this therapy is most appropriate for patients with bone lesions showing good uptake (>3:1) on nuclear scintigraphy and minimal soft tissue involvement or cortical lysis. Because the compound is a systemic therapy, it is an attractive option for dogs with multiple primary or metastatic lesions that cannot be addressed with surgery. A funded prospective clinical trial has just been completed by the author and others to assess the treatment of canine OSA using $^{153}\text{Sm-EDTMP}$ with or without carboplatin as a radiosensitizing agent, followed by standard cisplatin chemotherapy. We are also assessing protocols combining $^{153}\text{Sm-EDTMP}$ with external beam radiation and chemotherapy for curative-intent treatment of canine OSA, as well as alternative radiopharmaceutical agents with less myelosuppressive potential. Isolated limb perfusion with $^{153}\text{Sm-EDTMP}$ is also being evaluated at Colorado State University.

REFERENCES AVAILABLE UPON REQUEST