STAGING AND TREATMENT OF OSTEOSARCOMA

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Introduction

Osteosarcoma (OSA) is the most common primary bone cancer in dogs. Particular challenges identified by veterinarians dealing with this malignancy in daily practice include how to quickly and safely arrive at a definitive diagnosis, and how to develop a cost-effective and efficacious treatment plan.

Clinical Presentation

Osteosarcoma of the appendicular skeleton is considered to be a disease of middle aged to older dogs that are of large or giant breed. Because a slight peak in age incidence is reported for dogs from 18 to 24 months of age, some consider this disease to have a bimodal age distribution. One third of all appendicular OSA occurs in dogs weighing >40 kg, while smaller dogs are more likely to develop OSA of the axial skeleton. Breeds reported to be at greatest risk for development of appendicular OSA include Great Danes, Saint Bernards, Irish Setters, Doberman Pinschers, German Shepherds, and Golden Retrievers, although any large or giant breed dog should be considered at risk. Canine appendicular OSA has been reported to occur "away from the elbow and toward the knee". Although this adage certainly holds true for the two most common sites (the distal radius and proximal humerus), pelvic limb OSA is less likely to adhere to this adage. Common rear limb sites include the distal femur, distal tibia and proximal tibia. Overall, forelimb sites are more commonly affected than rear limbs and this is thought to be due to the fact that more weight is borne by the forelimbs. The metaphyseal region of long bones is the typical site for OSA development, thus lesions in epiphyseal or diaphyseal locations should raise an index of suspicion for alternative diagnoses. Common axial OSA sites, in descending order of incidence, include the mandible, maxilla, spine, cranium, ribs, nasal cavity and paranasal sinuses, and pelvis. Extraskeletal sites including the liver, kidney, spleen, adrenals, subcutis, mammary tissue, testicles, vagina, gastric ligament and eyes have been uncommonly reported.
**Diagnosis & Staging**

Primary bone cancer is a differential diagnosis that must be considered when dogs of typical signalment present with acute lameness and limb swelling, with no known history of trauma prior to presentation. Limb radiographs are often the first step in arriving at a diagnosis. The radiographic features of OSA range from osteolysis to proliferative responses typical of osteoblastic activity. The two classic radiographic appearances of OSA are:

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 tumor.

Neither radiographic sign is pathognomonic for OSA, but both can support a presumptive diagnosis. Other primary or metastatic bone cancer can mimic the radiographic appearance of primary OSA, as can osteomyelitis and some benign bone lesions. Diagnostic clues that support alternative diagnoses include joint involvement (typical of synovial cell sarcoma, not OSA), diaphyseal tumor location (more common with metastatic lesions) and "punched out" areas of lysis (typical of multiple myeloma). Bone biopsy is recommended for diagnostic confirmation and is indicated when it will change the treatment plan. Biopsy of a suspicious bone lesion must be done properly in order to maximize the likelihood of achieving a definitive diagnosis. Because the procedure carries with it some risk of bone fracture, a non-diagnostic specimen is an unacceptable outcome. Whereas veterinarians are generally trained to obtain skin biopsies from the border of normal and abnormal tissue, bone biopsy specimens should be obtained from the center of the lesion. Samples obtained from the periphery are more likely to yield a diagnosis of reactive bone. Alternatively, fine needle aspiration and cytology may provide clues to help differentiate neoplastic from non-neoplastic causes of bone lesions, although the accuracy rate is lower with this method. New tools such as immunocytochemistry to detect alkaline phosphatase in cytology samples are currently under investigation as ways to improve the accuracy of cytological examination for OSA.

Tumor staging, which refers to the process of determining the disease extent within the patient, is an important step in 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 orthopedic examination to assess for other limb involvement, and long bone radiographs or bone scan to assess for other bone involvement or concurrent orthopedic diseases are warranted. Interestingly, one author reported a greater likelihood of detecting other primary or metastatic lesions on bone survey radiographs than on thoracic films. Other pretreatment patient assessments should include a complete physical exam with particular attention to orthopedic, cardiac and neurological evaluation, a complete blood count to assess for underlying infectious disease and to determine if surgery and chemotherapy are feasible, and a 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**

Several treatment options are available for the management of canine appendicular OSA. The choice of treatment should be tailored to each individual patient and should take into consideration the patient's weight, orthopedic and neurologic status, degree of lameness and cortical bone destruction, tumor 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
2. Control or slowing of metastatic disease.

In general, a combined modality approach is necessary to achieve both of these goals. A summary of indications, contraindications and anticipated outcome for some of the currently available treatment options for OSA is provided below.

**Amputation Alone**

Limb amputation is likely to provide rapid pain relief, assuming there are no other concurrent bone lesions and the patient is orthopedically and neurologically stable. Without adjuvant therapy to address micrometastatic disease, amputation is considered to be 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 combined approach to treatment using amputation and chemotherapy is currently considered the 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. Potential toxicities associated with the commonly used chemotherapy agents range from nephrotoxicity (cisplatin and, to a lesser degree, carboplatin) to cardiotoxicity (doxorubicin). Cost is also a common consideration.
when deciding which chemotherapy agent will be used. Reported survival times for amputation and chemotherapy are summarized in Table 1.

Since the publication of the above-referenced reports, the efficacy of single-agent carboplatin and the doxorubicin/cisplatin protocol have been questioned. As a result, re-evaluation of both protocols have been undertaken and updates will be provided.

The best time after amputation to start chemotherapy is a compromise between allowing time for recovery from surgery and not allowing time for micrometastases to grow. In one study, chemotherapy was delayed for either 2 days or 10 days after amputation. No difference in survival was seen regardless of the delay, but there was increased toxicity seen in the dogs treated 2 days after surgery. Most oncologists agree a delay of two weeks between surgery and starting chemotherapy is acceptable.

**Limb-sparing Procedures**
The term "limb-spare procedure" may refer to a surgery to remove diseased bone and replace it with a cortical allograft, or it may simply refer to any procedure short of limb amputation. Limb-sparing surgery to remove affected bone and replace it with an allograft may be a reasonable option for dogs that are poor candidates for amputation, provided the clients fully understand the potential benefits and complications of this procedure. For dogs that are good candidates for amputation, limb-sparing surgery may not be the best treatment choice. While limb function is improved in the majority of dogs after limb-sparing surgery, post-operative complications such as osteomyelitis occur in roughly 1/3 of all dogs undergoing the procedure. It is interesting to note that dogs undergoing limb-sparing procedures fare better in terms of overall survival if their surgical site becomes infected.

**Radiation Therapy**
External beam radiation therapy may provide pain palliation for dogs with appendicular OSA. When used in this palliative-intent setting, radiation is typically delivered on a Day 0-7-21 or a Day 0-7-14-21 protocol 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. It is hoped that these techniques will provide a more effective means of utilizing radiation for local control, not just palliation, of OSA.

**Palliative Therapy**
1. NSAID therapy: carprofen 2.2mg/kg BID PO; piroxicam 0.3 mg/kg daily or every other day PO; deracoxib 1-2 mg/kg/day PO; Etodolac 10-15 mg/kg/day PO; meloxicam 0.05-0.1 mg/kg/day PO; ketoprofen 0.5-1.0 mg/kg/day PO
2. Morphine sulfate tablets 0.5-2.0 mg/kg QID PO
3. Tramadol 1-2 mg/kg BID to TID PO
4. Fentanyl patch 50 ug/hr q 72 hours (10-20 kg), 75 ug/hr q 72 hours (20-30 kg), 100 ug/hour q 72 hours (> 30 kg)
5. Amantadine 3-5 mg/kg QD PO
6. Pamidronate 1-2 mg/kg IV administered over 2 hours in 250ml of saline Q28D
7. Gabapentin 10 mg/kg BID PO

**References Available Upon Request**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>1-yr Survival Rate</th>
<th>DFI (days)</th>
<th>MST (days)</th>
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<tbody>
<tr>
<td>Cisplatin Single Agent</td>
<td>38% - 62%</td>
<td>165 – 226</td>
<td>262 – 413</td>
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<td>Carboplatin Single Agent</td>
<td>35.4%</td>
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<td>Doxorubicin/Cisplatin</td>
<td>NR to 48%</td>
<td>NR to 470</td>
<td>345 – 540</td>
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<tr>
<td>Doxorubicin/Carboplatin</td>
<td>NR</td>
<td>202</td>
<td>202</td>
</tr>
</tbody>
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DFI: Median Disease Free Interval
MST: Median Survival Time
NR: Not Reported

Table 1: Reported Responses to Common Chemotherapy Protocols for Canine Osteosarcoma

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- Tues. Oct. 10, 2006 at 7pm at Mass Vet Referral Hospital in Woburn
  Staging and Treatment of Osteosarcoma presented by Michael Buss, DVM, MS, DACVIM (Oncology)

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