

## **OSTEOSARCOMA**

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Osteosarcoma is a disease that has seen great treatment advances in the past few years. Most primary bone tumors occur in giant breed or large breed dogs although the disease can occur in smaller dogs. The median age of dogs affected with osteosarcoma is around 10 years, with a subset of tumors arising in younger dogs (18-24 months). No sex predisposition is noted. Rapid early growth and increase in stress on weight-bearing limbs are cited as reasons for this predisposition. Osteosarcoma is also associated with healed fracture sites or internal fixation devices, suggesting that excessive cell replication caused by chronic irritation can play a role in the onset of these tumors.

The term osteosarcoma is synonymous with osteogenic sarcoma, meaning bone-forming tumor. These tumors are characterized by the formation of osteoid bone matrix material. Canine osteosarcoma can vary in the type and quantity of matrix produced and cell arrangement resulting in osteoblastic, chondroblastic, fibroblastic, undifferentiated and telangiectatic (vascular) subclassifications. These patterns may vary from tumor to tumor or even within the same tumor. Hence, small biopsy samples may be misdiagnosed as chondrosarcoma, fibrosarcoma or hemangiosarcoma. It is therefore important to obtain follow-up histologic analysis of the entire tumor following surgical therapy.

Seventy-five percent of osteosarcomas occur in long bones, with 25% arising in the flat bones of the skull or axial skeleton. Most tumors occur within the medullary cavity in metaphyseal sites, with distal

radius, proximal humerus, proximal or distal femur, or proximal or distal tibia being most commonly affected sites. Historically, dogs may show an intermittent lameness that is due to subperiosteal bleeding and microfractures intermittently. As the disease progresses, swelling and lameness become more obvious. These lesions are quite painful and pathologic fractures can occur.

### **MOLECULAR PATHOGENESIS**

As molecular genetic studies have progressed in veterinary and human oncology, several factors have emerged as being important in osteosarcoma. Some findings have yet to be identified in canine disease and are extrapolated from the human counterpart, for which canine tumors are a very useful clinical model. From the perspective of oncogene and growth factor pathway derangements, there is mounting evidence that a variety of genes can be involved, including the pathways of the Met oncogene, platelet derived growth factor (PDGF), growth hormone and insulin growth factor pathways. Tumor suppressor gene derangements include alterations in p53, pRB, and most recently PTEN. Osteosarcoma cells are immortalized by upregulation of telomerase enzyme expression in some cases, but also by the ALT mechanisms, which involves end-chromosomal fusions or chromosomal translocation, and ensuing genomic instability with profound aneuploidy the result. Bone tumors are highly metastatic because of inherent expression of enzymes important to bone matrix remodeling, such as matrix metalloproteinases, as well as derangements in pathways involving cytoskeletal stability such as defects in ezrin signaling. Apoptosis defects in osteosarcoma cells arise from unopposed AKT signaling due to PTEN deletions, as well as

p53 mutation and MYC overexpression.

## **DIAGNOSIS**

Radiographs of these lesions reveal tumors that may be primarily lytic, blastic or mixed in appearance. The classic radiographic signs of cortical lysis, periosteal spicules in a "sunburst" pattern, and periosteal lift(Codman's triangle) can be seen. Osteosarcomas do not cross joints, with articular cartilage providing the physical barrier. These lesions are virtually always solitary. Evidence of multiple bone lesions would suggest metastatic neoplasia or infection. Differential diagnoses for these lesions would include other primary bone tumors such as chondrosarcoma, fibrosarcoma, and hemangiosarcoma. Tumors of bone marrow origin such as multiple myeloma and lymphoma, tumors that are metastatic to bone (mammary and urogenital carcinomas) and bacterial and fungal osteomyelitis must also be considered.

### **Biopsy**

Often the diagnosis of osteosarcoma is a presumptive one based on the signalment, history and radiographic appearance of the lesion. Bone biopsy can be very valuable in situations when the potential for mycotic diseases of bone exist. A Jamshidi bone marrow biopsy instrument or trephine biopsy is recommended. Risks of biopsy include fracture of an already weakened bone, and obtaining a non-diagnostic sample of reactive bone and potential for seeding the tumor. We have found that fine needle aspiration can be highly successful in diagnosis of osteosarcoma. Immunocytochemistry with an alkaline phosphatase stain can also be used to support the diagnosis of osteosarcoma with fine needle aspirates.

## **Staging**

Staging evaluation of these patients includes a minimum database, as these dogs are older and may have concurrent organ impairment. Thoracic radiographs are also taken to screen for any distant metastasis. In reality, the presence of measurable metastasis at the time of diagnosis is rare, but it is estimated that 90-95% of dogs have micrometastasis at the time of diagnosis. Some authors advocate performing a radionuclide bone scan or survey radiographs of bones to detect bone metastasis or synchronous primary lesions. In a Colorado State study, 6.4% of 171 dogs had bone metastasis at diagnosis (detected by survey radiographs) as compared to 4% with chest metastasis at diagnosis. Radionuclide scans may introduce the problem of false positive results, as any inflammatory lesion or injury (degenerative joint disease or tooth root abscess, for example) may "light up" on a bone scan.

## **PROGNOSTIC FACTORS**

Prognostic factors include the age of the dog at diagnosis. Dogs between the ages of 7 and 10 years survived longer than older or younger dogs in one study. Total serum alkaline phosphatase and bone alkaline phosphatase levels can also be prognostic for osteosarcoma. Dogs that had elevated total alk phos and bone alk phos levels prior to surgery had shorter survival and disease free interval. Some authors feel that size of the primary tumor at the time of diagnosis is also prognostic. One study suggests that increased percentage of bone necrosis following doxorubin therapy correlated with increased survival. Dogs with the rare variant of parosteal osteosarcoma (surface as opposed to within the medullary cavity) have better cure rates than dogs with standard osteosarcomas. A

recent study revealed that osteosarcomas may be positive by immunohistochemical staining for COX-2 expression, but most such staining was of low intensity. Those dogs with high intensity staining for COX-2 had a poor outcome. Axial skeletal osteosarcomas have relatively lower rates of distant metastasis than do appendicular osteosarcomas, especially the ones of mandibular origin. Regional node metastasis, although relatively rare (4,4% in a recent study), appears to be a significant negative prognostic indicator for disease free interval and survival.

## **THERAPY**

There are two critical areas of importance in the treatment of osteosarcoma. Several options now exist for treatment of the primary lesion, and treatment of distant metastasis has improved and advanced over the past few years.

### **Surgery**

Treatment of choice for a primary osteosarcoma lesion of the long bone remains amputation. Amputation alone gives a median survival time of about 4-5 months, and obviously provides palliation of bone pain and prevents pathologic fracture. Amputation is usually curative with regard to the local tumor, except in cases of proximal femoral or proximal humeral lesions with extensive soft tissue involvement, where stump recurrence can occur. Surgical excision is indicated for lesions of the flat bones as well, where practicable.

### **Limb-sparing**

procedures in dogs are relatively new, and are available at an increasing number of referral centers. The goals of limb sparing are to obtain local tumor control, provide a pain-free and functional limb, and

not diminish long-term survival. The most commonly performed procedure involves chemotherapy and/or radiation followed by surgical excision of the tumor and replacement of the bone with an allograft. Allograft infection is the most frequent complication in these patients, necessitating amputation. Limb function can be good to excellent in 80% of the cases, with better limb usage observed in dogs with forelimb sparing procedures. One and 2 year survival is comparable to that achieved by amputation combined with chemotherapy, and is better than amputation alone.

Recently, trials of a technique referred to as bone transport osteogenesis have been used for limb sparing of lesions in the distal radius. In this procedure, the diseased portion of distal radius is resected and an osteotomy incision is made in unaffected bone proximal to the diseased bone that has been removed. A ring fixator with a sliding segment can then be advanced at a rate of 1mm per day, to allow for new bone formation in the osteotomy site. Ultimately, the new bone docks with the residual distal radius, and the joint can then be fused. This procedure has the advantage of avoiding allograft infection, but is still investigational.

Another form of limb-sparing surgery under investigation for lesions of the distal radius is the vascularized ulnar transposition. In this procedure, the neoplastic segment of the distal radius is resected, and the unaffected adjacent distal ulna is rotated into the bone defect created. The graft is stabilized by a buttress plate applied with carpal joint fusion. If the vasculature to the ulnar transport segment can be maintained, the resulting graft heals as a fracture would. In the case of allograft limb-sparing, the dead bone segment is not revascularized and can act as a sequestrum and nidus for infection.

Finally, autotransplant with pasteurized bone taken from the tumor site is being investigated. Local implant failure is a problem for the vascularized ulnar transposition and autotransplant procedures.

Aggressive excision may be performed on osteosarcomas of the axial skeleton, however, local control is difficult to achieve, and long-term survival is poor. In a series of dogs with osteosarcomas of the ribs and pelvis, few dogs survived more than 4 months after diagnosis. Combined modality therapy may offer the best prognosis.

### **Radiation Therapy**

The use of radiation therapy in a palliative setting has provided an alternative to traditional amputation. In several studies, the administration of 10Gy fractions on a 0, 7, 21 day schedule with cobalt radiation therapy has provided an acceptable level of pain control. Approximately 70 to 90% of the patients will achieve increased limb function or stable orthopedic disease, that is durable for 3-4 months. Overall survival times are similar to those achieved by amputation alone, but occasionally dogs can undergo more than one course of palliative radiation and achieve a second period of stabilization. A recent study reported the use of four 8 Gy fractions of cobalt irradiation to 24 dogs with axial or appendicular OSA. In this trial, the 4-fraction protocol was associated with a 92% response rate, which was superior to the response rate achieved by 3 large fractions. Chemotherapy (cisplatin or carboplatin) may also be given with the radiation therapy and this may increase the level of pain control but has no substantial effect on overall survival times. Therapy with bone localizing radio-isotopes such as samarium are being explored in veterinary oncology as well.

## **Medical Palliation**

In some situations, owners wish to make the dog diagnosed with osteosarcoma comfortable for short periods of time. This may be accomplished through the use of analgesic medications, such as NSAIDs and narcotic-type analgesics. Interestingly, NSAIDs may have a therapeutic effect in more aggressive OSA lesions, as short survival time was associated with high levels of COX-2 expression in one study. This finding would need to be validated with a prospective trial, however. There are other potential agents that may be given for the palliation of OSA. Bisphosphonates are synthetic analogs of inorganic pyrophosphate (PPI) and possess the ability to inhibit calcium phosphate precipitation in vitro and biologic calcification in vivo. Bisphosphonate compounds inhibit osteoclast resorption of the mineral matrix of bone by directly binding to hydroxyapatite; these agents were initially employed for the adjunctive treatment of osteoporosis. It has been demonstrated that bisphosphonates can trigger apoptosis in normal osteoclasts, and recent in vitro work suggests that they may induce cell death in canine malignant osteoblasts in vivo. There are now 3 generations of compounds in this class. The use of a second-generation drug called pamidronate (Aredia), has become a standard of therapy for humans with metastatic bone carcinoma. This treatment option in humans offers decreased pain, fewer fractures and increased bone remodeling/healing and thus an overall improved quality of life. Metastatic skeletal carcinoma is very different from the spontaneous primary osteosarcoma lesions that occur in dogs. It is currently unknown if the administration of bisphosphonates will offer palliation to dogs with osteosarcoma, but response to initial use of this compound has been encouraging. In a recent study involving

administration of pamidronate in dogs with primary or metastatic bone tumors, 4 out of 10 animals with osteosarcomas achieved better pain control. A third generation bisphosphonate called .zolendronate has substantial increased potency in blocking bone resorption, and is being evaluated in bench and clinical trials. Further studies are needed to fully evaluate the therapeutic potential of these treatment options in dogs. For some types of tumors evaluated, such as multiple myeloma, bisphosphonates have a direct cytotoxic effect on the cancer as well as a bone sparing effect. Early evidence suggests that this may be the case in canine OSA as well, at least in cell culture studies.

### **Chemotherapy**

Control of distant metastasis is best accomplished by adjuvant chemotherapy. The drugs that have shown the greatest efficacy against canine osteosarcoma are doxorubicin, cisplatin and carboplatin. These drugs may be used as a single agent or used together in combination protocols. Cisplatin treated dogs have a median survival time ranging from 260-400 days with 30-62% survival at one year and 6-21% survival at two years. Cisplatin must be given with rigorous saline diuresis to avoid nephrotoxicity. In dogs with preexisting renal and/or cardiac disease it should be used with extreme caution. Carboplatin appears to be as effective as cisplatin in treating osteosarcoma. In one study, dogs treated with carboplatin had a median survival time of 321 days with 35% of the dogs alive at one year. Smaller dogs had longer survival times in this study. Carboplatin's most common side effect is myelosuppression. Doxorubicin therapy biweekly for a total of 5 doses with 2 or 3 doses prior to amputation and the remainder given after surgery had similar survival times. Median survival times of 366 days with 50% alive at one year and 10% alive at two years have been reported.

Chemotherapy protocols that combine cisplatin and doxorubicin also have been used. One protocol alternated cisplatin and doxorubicin every 21 days for 2 cycles of therapy. Median survival in this study was about 300 days with 37% alive at one year and 26% alive at two years. A recent article evaluated the alternating use of carboplatin and doxorubicin in canine OSA patients. Using 300mg/m<sup>2</sup> carboplatin IV alternating with 30 mg/m<sup>2</sup> doxorubicin on a 21 day cycle interval resulted in a median progression free survival of 227 days, with overall survival of 320 days. One-year survival was 48% and 2-year survival was 18% for the 32 dogs evaluated in the study. Toxicities were mild to moderate using this protocol. The recent availability of generic carboplatin should result in this protocol becoming more cost effective for clients. As carboplatin is administered as a simple IV bolus, it is superior to cisplatin for use in private veterinary practice because of the extensive fluid diuresis required for cisplatin renal protection.

In another study, cisplatin and doxorubicin were given on two consecutive days (Cis on day 1, doxo on day 2) every 21 days for 4 cycles. The dose of doxorubicin was decreased in this study to avoid myelosuppression. In the initial pilot study of 16 dogs treated with this protocol, median survival time was 534 days with 79% alive at one year and 45% alive at two years. Unfortunately, a larger follow up study of 34 dogs failed to reveal this long survival median, and it was discovered that the protocol yielded a median disease free survival of 330 days and overall survival of 300 days. This larger prospective study cohort suffered from substantial toxicity as well, with severe toxicity in 7 of 34 cases and 3 chemotherapy-induced deaths. It is interesting to note that the initial cohort of 16 dogs

treated with this protocol were also given empty liposomes as part of a control group for an immunotherapy trial. While the empty liposomes did not contain active immunomodulatory compound muramyl tripeptide, it is possible that macrophage activation was achieved by the liposomes alone. This trial should be repeated in a larger cohort of dogs with the administration of liposomes, as the initial pilot study was not precisely replicated in the larger dog trial that followed.

An alternative method to deliver cisplatin uses an open polylactic acid sponge that contains cisplatin (OPLA-Pt). This method allows for a slow, time release of cisplatin. This causes an increased area under the curve (AUC) that allows for longer exposure of the drug. This approach may provide better local tumor control when used in limb-sparing surgery, without increasing the side effect risk of the systemic chemotherapy. The use of chemotherapy before amputation (neoadjuvant therapy) will allow the pathologist to assess for evidence of tumor necrosis, which may be a prognostic indicator in survival as well as the ability of the chemotherapy to control the metastatic disease. The newest chemotherapy agent to be applied to veterinary OSA patients is a drug called Ifosfamide, which is a new generation cyclophosphamide analog. This drug has myelosuppression, renal toxicity, and urothelial injury as common adverse effects. To combat both renal insufficiency and sterile hemorrhagic cystitis, the drug is administered along with the uroprotective agent MESNA in a fluid diuresis protocol. Ifosfamide has been added to several standard-of-care human OSA protocols, but we are still deliberating about the best way of incorporating this agent into canine OSA combination chemotherapy treatment.

## **Metastatic Disease**

Virtually all osteosarcomas are metastatic at the time of diagnosis. However, the micrometastatic disease can be managed with chemotherapy. Life is prolonged over what would be the case with surgery alone with a modest number of dogs (10-20%) living beyond 2. years. Once gross metastatic disease is visible on the radiographs, it is rare that chemotherapy is capable of inducing a response. It is possible for a select population of patients to undergo a metastasectomy of the pulmonary nodules, which has been reported to result in a median additional life prolongation of about 6 months. Indications for metastasectomy are low numbers of detectable lesions (3 or less), slow growth or stable diseases over a 30-day observation period, and absence of detectable extrapulmonary metastasis. Some human and canine patients have been cured by metastasectomy as a salvage procedure, but the majority of .dogs will ultimately succumb to their disease.

### **TABLE I -OSTEOSARCOMA CHEMOTHERAPY**

#### **Pre-diuresis Cisplatin Administration Protocol**

18.4 ml/kg/hour 0.9% saline IV for 4 hours

Premedication with antiemetics:

(Give before starting cisplatin infusion)

Torbugesic 0.4 mg/kg IV

or

0.1 mg/kg metaclopramide (Reglan) IV

0.25 mg/kg dexamethasone sodium phosphate IV

#### **Cisplatin therapy:**

Administer cisplatin 50-70 mg/M<sup>2</sup> in 100 ml 0.9% saline IV over 20

minutes.

**Post-diuresis:**

18.4 ml/kg/hour 0.9% saline IV for 2 hours

Note: If vomiting is seen, it will typically occur around the end of the post-diuresis period. Reglan may be repeated at this time, and the rare case with extreme vomiting may benefit from oral Reglan after discharge for the first 24 hours after cisplatin therapy

**Alternating Cisplatin/Doxorubicin Protocol**

Doxorubicin 30 mg/M<sup>2</sup> IV Day 1

Cisplatin 60 mg/M<sup>2</sup> IV (administer as above) Day 21

Repeat cycle 1 time.

**Alternating Carboplatin/Doxorubicin Protocol**

Carboplatin 300 mg/M<sup>2</sup> IV Day 1

Doxorubicin 30 mg/ M<sup>2</sup> IV Day 21

Monitor CBC before and 8-10 days after each drug.

Monitor serum chemistry panel before the 2nd and 3rd dose of carboplatin.

Repeat cycle 3 times.

**Combination Cisplatin/Doxorubicin Protocol**

Cisplatin 50 mg/M<sup>2</sup> IV (administer with diuresis above) Day 1

Doxorubicin 15 mg/M<sup>2</sup> IV Day 2

Repeat cycle Q 21 days for 4 - 6 cycles

**Carboplatin**

Carboplatin 300 mg/M<sup>2</sup> IV every 21 days for 4-6 treatments

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**Research Interest:** Spontaneous animal  
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