O – Oncology

KEY SURGICAL, MEDICAL ADVANCES FOR TREATING OSTEOSARCOMA

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Introduction

Osteosarcoma (OSA) is the most common bone tumor in dogs and is characterized by a highly invasive and metastatic behavior. The tumor is less common in cats. This tumor frequently affects middle-aged, large breed dogs (less than 5% occur in breeds smaller than 12 kg) and arises in 75% of cases in the metaphyseal area of bones of the appendicular skeleton. The median age of dogs with OSA is 6-7 years. Males are more commonly affected than females. A cause for OSA is unknown although many etiologies have been stipulated (radiation, microtrauma, genetics, implants, nutrition). Most cats are older and a higher number of OS arose from extraskeletal sites (38%).

Pathology

OSA is a malignant spindle-cell tumor characterized by direct formation of bone or osteoid tissue by tumor cells. OSA is an aggressive tumor with a locally invasive behavior and a high rate of metastasis and can be subdivided in chondroblastic, osteoblastic, fibroblastic, telangiectatic, and mixed type tumors. Common locations for OSA include the distal radius, proximal humerus, distal femur, proximal tibia, distal tibia, proximal femur, ulna and scapula. The remainder of OSA (25%) occurs in the axial skeleton (mandible, maxilla, vertebrae and ribs). Multicentric OSA is rare (< 10% of cases). Fifty-five percent of feline OS occur in the appendicular skeleton. OS Pulmonary metastases are present in more than 90% of the patients at time of initial diagnosis. The prognosis for dogs with OSA without therapy is poor, less than 5% will survive longer than one year after diagnosis. The prognosis for cats seems to be better, but small numbers have not allowed a good scientific comparison between groups.

History, clinical signs, and differential diagnosis

Dogs and cats with OS are often presented with an acute or chronic lameness and a visible swelling at the affected site. The owner often backdates the lameness to a minor traumatic incident and pain can be elicited upon palpation. Muscle atrophy, a history of progressively decreased weight bearing, and pathologic fractures may be present. Differential diagnoses include other primary bone tumors (fibrosarcoma, chondrosarcoma, etc.), metastatic tumors (especially in cats), bone cysts and bacterial or fungal osteomyelitis.

Diagnosis

The presumptive diagnosis of a bone tumor is easily obtained by regional radiography. Radiographic changes include a mixed pattern of osteolysis and bony proliferation and either change can predominate. Macroscopic pulmonary metastases (> 5 mm) are evident in 10% of cases at initial radiographic examination. Metastatic nodules have the 'canon-ball' appearance and are often located in the periphery. Feline pulmonary metastases can have a miliairy pattern. The definite diagnosis is obtained by bone biopsy and histologic examination. The biopsy can be performed using a Jamshidi biopsy needle or Michele bone trephine. Two biopsy specimens, one obtained from the centre and one from the tumor-normal tissue transition zone, will allow proper diagnosis in 92% of cases. Additionally, scintigraphy may be used to diagnose multicentric or metastatic OS. However, scintigraphy will not differentiate benign (non-tumorous) from malignant lesions, and should be followed by radiography of regions with increased uptake. CT- and MRI-scans can be used to estimate the extent of bony and surrounding soft tissue involvement.

Histology

Evaluation of the histologic characteristics of OS substantiated the importance of tumor grading. Dogs with more aggressive tumors (grade III) had a worse prognosis after multivariate analysis compared to dogs with lower grade tumors. Also, preoperative, non-steroid-induced plasma alkaline phosphatase elevation was associated with a poor prognosis. Comparisons for cats are researched at this moment.

Genetic alterations

Canine OS contain genetic alterations comparable to human OS. P53 mutations were common (42%) and were associated with poor outcome using multivariate analysis. Most alterations consisted of point mutations.

The role of growth hormone (GH) expression within the tumor is unclear. After we determined that local GH expression is present in 25% of the dogs, a large number of dogs were evaluated for the clinical importance of this finding. Local GH expression was associated with a poor prognosis. Local GH production may indicate the presence of an autocrine phenomenon, in which the tumor stimulates itself.

Therapy

Successful treatment of OS includes local tumor control as well as the treatment of systemic tumor spread. Local marginal resection as sole treatment will result in high recurrence rates, dysfunction of the leg and undiminished metastatic spread of tumor and should be avoided if adjunctive therapy is not available. In dogs, amputation alone provides good primary local tumor control, but otherwise does not prolong survival time. A median survival time of 19 weeks is observed after amputation. More than 90% of these dogs will die within a year because of the development of distant metastases. After amputation, recovery from surgery and adaptation to three legs is fast. Most dogs, even the larger breeds, function extremely well three-legged and most owners are satisfied with the animal's quality of life. Recovery after amputation is faster than many owners expect. Most dogs are at ease with walking on three legs within a month and dogs with bone tumors are able to ambulate well within 7 days. The owner's satisfaction with the procedure is very high and complications are rare. Force plate analysis of amputees showed significant changes in ground reaction forces. Dogs with front leg amputations may have more problems recovering after the surgery in the beginning because of these GRF changes. Cats seem to have not problem with walking on three legs and thus amputation is the therapy of choice in appendicular OS.

Amputation in combination with chemotherapy enhances survival in canine OS because it decreases the occurrence of metastases. The best-known chemotherapeutic agent, cisplatin, has been shown to significantly prolong the disease-free intervals and survival times in dogs, and remains the drug of choice. Cisplatin is administered intravenously at 60-70 mg/m^2 for 4-6 doses, at three-week intervals. Cisplatin is associated with the risk of severe side effects (nephrotoxicity, gastrointestinal toxicity, myelosuppression, and ototoxicity) if given as a sole agent. Most side effects can be prevented by a concurrent 4-hour saline diuresis protocol; however, mild vomiting and bone marrow suppression often will occur. Median survival intervals of dogs treated with cisplatin chemotherapy and resection of the primary tumor is significantly higher than dogs without chemotherapy. A one-year survival percentage of 45-55% has been reported. The median survival interval of dogs treated with chemotherapy before resection of the primary tumor compared to postoperative chemotherapy was not significantly different. Also, the route of administration (IV versus IA) did not influence survival. Dogs that receive more than three doses of cisplatin will survive longer than dogs that receive two or less. Currently, it is recommended to give at least four doses of cisplatin.

Other agents, used for canine OS, that have shown a beneficial effect include doxorubicin, liposome encapsulated muramyl tripeptides (liposome/

MTP) and carboplatin. Doxorubicin has been shown to prolong survival in combination with cisplatin and as single agent. Dogs treated for OS with liposome/MTP survived significantly longer than those treated with placebos. Carboplatin, a second-generation platinum compound, does not induce nephrotoxicity and can be given as a 15-minute bolus injection without saline diuresis. Carboplatin significantly increased survival times compared to dogs with amputation alone and was comparable to cisplatin chemotherapy. Carboplatin is given intravenously on an every 21-day schedule at 300 mg/m$^{2.}$

Instead of amputation, local control may also be obtained by limb-sparing procedures. The goal of limb sparing is to obtain local tumor control, while providing a pain-free and functional leg. The procedure usually involves (marginal) local surgical excision of the tumor in combination with chemotherapy or radiation therapy. Common locations amenable for performing limb sparing are the distal radius, proximal humerus, scapula and ulna. OS of the distal radius and proximal humerus are removed by marginal resection, replaced by an allograft and affixed to the host bone using a bone plate. Arthrodesis of the adjacent joint is often necessary. Recovery after surgery is often fast with dogs bearing weight within a week. Eighty percent of dogs return to normal function after limb-sparing procedures in 6-8 weeks. OS of the ulna and scapula may be resected without the use of an allograft. Ulnectomies distal to the elbow joint and partial scapulectomies are extremely well tolerated. Complications associated with limb-sparing procedures include infection, recurrence and implant failure. The use of cemented allografts has decreased the number of complications associated with allograft failure significantly.

The incidence of local tumor recurrence after limb sparing varies between 25-50%. Methods to prevent local recurrence include preoperative radiation and preoperative administration of chemotherapy by intra-arterial route, local intravenous perfusion, or slow release polymers. Any of these therapies should be considered in tumors that have extended through the bony cortex and have invaded in the surrounding soft tissues. The use of intravenous, systemic chemotherapy has been unrewarding in preventing recurrence after incomplete resection.

In cats, the advantage of adjunctive therapy after surgical excision is unclear. Some authors clearly state that feline OS behave comparable to canine while others debate the effectiveness of chemotherapy in the cat. One thing is for sure, however, cats are extremely sensitive for cisplatin and life-threatening pulmonary edema occurs after administration of this drug.

Metastatic osteosarcoma

OS is a highly metastatic tumor and most metastases are observed in the lungs. Macroscopic metastatic disease in canine OS is not responsive to chemotherapy and the prognosis is often poor. Surgical resection of pulmonary metastasis is useful in limited numbers of patients if less than three nodules are present, if the tumor size has not doubled in a month, and if the disease-free interval is longer than 300 days from the initial date of diagnosis. No data are available for cats concerning metastatectomy in cats.

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