A REVIEW AND WHAT'S NEW IN CANINE OSTEOSARCOMA

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INTRODUCTION

Osteosarcoma (OSA) is a highly malignant tumor that has both a locally invasive and highly metastatic biologic behavior. Multimodality therapy must be employed to provide patients with this cancer the best chance for improved quality and quantity of life. Despite these therapies, however, dogs with OSA generally succumb to their disease within 6-12 months. This presentation will highlight new information regarding diagnostics and therapeutics for this aggressive cancer.

Appendicular OSA is the most common primary bone tumor in dogs, accounting for up to 85% of all primary bone tumors. There is a bimodal peak in age of occurrence, at 2 years of age and middle-aged to older dogs. Males are reported to be over-represented with a male:female ratio of 1.5:1. Large to giant breed dogs are at greater risk with Irish setters, St Bernards, Rottweilers, etc. likely to be affected. One study found a mutation in a proto-oncogene (MET) in 70% of Rottweilers; this mutation was found in < 5% of all other breeds examined. This breed-specific finding suggests a heritable mutation within the Rottweiler breed. Additionally, a recent abstract discussed differential expressed of miRNAs (short RNA molecules which generally lead to gene silencing, dysregulated miRNAs have been associated with cancers) in greyhound vs Rottweiler tumors. This early finding supports another breed-specific reason for the development and possibly progression of OSA. Ongoing studies are evaluating more breeds for miRNA expression within OSA tumors.

DIAGNOSTICS

Radiographs of the primary lesion will show a mixture of bone proliferation and lysis; the degree of each finding can vary widely between tumors. The metaphyseal regions of the long bones are the most frequent locations for the tumors: away from the elbow, but towards or away from the knee (i.e. in the rear leg the tumor may arise at either end of the femur or tibia). Thoracic radiographs will show metastasis in only ~8% of dogs at diagnosis, but microscopic metastasis is present in another 80%. Finding visible metastatic lesions greatly changes the prognosis, as visible nodules do NOT respond to standard chemotherapy (see below for metronomic chemotherapy). Thus, a complete metastasis check with 3 radiographic views (right and left lateral and a DV) is critical. CT scan is a more sensitive way to detect nodules; in a retrospective study of 39 dogs with OSA, 5% (2 dogs) had radiographically visible pulmonary nodules, while 28% (11 dogs) had CT visible nodules. However, at this time, the response to chemotherapy of CT visible yet non-radiographically visible nodules is unknown (i.e. how do CT visible nodules affect prognosis with treatment?).

Fine needle aspirates of the bone lesion may be diagnostic in the majority of cases. OSA often is easily exfoliative and reveals large, immature mesenchymal cells that may be producing osteoid (pink matrix). OSA may have a plasmacytoid appearance, with round-ish margins and deep blue cytoplasm. Alkaline phosphatase staining is a highly sensitive and specific way to determine if a malignant cell is of bone origin. If cellularity is poor, a biopsy may be needed. The least invasive technique is with a Jam Shidi bone core biopsy instrument; most dogs are not significantly more lame after this type of biopsy.

The minimum data base may reveal several factors that carry prognostic significance. Serum alkaline phosphatase is prognostic: dogs with elevated levels have shorter survival times by 50% even when treated aggressively with surgery and chemotherapy. Also, a recent study showed that higher numbers of blood monocytes ($>0.4x10^3$) and/or lymphocytes($>1.0x10^3$) prior to amputation and chemotherapy carried a worse prognosis. The disease-free interval (DFI) of dogs with monocyte numbers above the median was 200 days, vs 595 days for those below the median ($p<.002$). The DFI for dogs with lymphocytes above the median was 221 days, vs 470 days for those below the median ($p<.03$).

TREATMENT AND PROGNOSIS

Another prognostic factor supported by several reports is tumor location, with proximal humerus carrying a worse prognosis. Some studies show that young age is worse, yet more recent studies argue against that finding.

DEFINITIVE THERAPY

The treatment option associated with the longest disease control and overall survival times is surgical amputation followed by 4 to 6 doses of a platinum based chemotherapy drug (cisplatin or carboplatin). A recent study showed no improvement in outcome in dogs receiving 6 doses of carboplatin vs 4 doses. Doxorubicin may also be used; it may be slightly less effective. With amputation alone, median survival times (MST) range from 4-6 months; chemotherapy post-surgery will extend that to 10-12 months. While combination chemotherapy would seem to offer benefits over single-agent treatments, no studies to date have shown strong support for the use of combination chemotherapy. MST with such combinations remain similar to single agent treatments, and toxicities are higher. As an alternative to amputation for local tumor control, limb salvage surgery, which remove the tumor but spare the limb, can be effective for tumors at the distal radius. Good candidates for limb salvage are dogs with the tumor confined to the bone (minimal extension into adjacent soft tissue) and involving less than 50% of the bone length.

High dose radiation (~36 Gy total) extremely precisely delivered to the tumor in 1-3 doses can be used with a curative intent and is a type of limb-salvage procedure. Such high dose radiation is termed stereotactic radiosurgery (SRS) when the treatment is given all in 1 dose, and stereotactic radiotherapy when given in 2-3 doses. SRS was reported in 2004 in 11 dogs with good clinical results and minimal side effects. Pathologic fracture occurred in 4 dogs and was surgically stabilized. The MST was 363 days. Results from the use of SRT and adjuvant carboplatin chemotherapy from over 50 treated dogs were recently discussed at a national meeting. Most of the dogs received the radiation in 3 doses. The clinical responses were good to excellent. MST was 275 days (range 66-723). Most of the dogs died of metastatic disease. Pathologic fracture was seen in only 16% of cases, and the researchers have identified factors found in the imaging of the tumor that correlate with increased potential for fracture. In these cases, prophylactic surgical stabilization immediately after the final radiation dose is being offered. One advantage to SRT limb salvage over surgical limb salvage is the ability to treat tumors in sites other than the distal radius.

IMMUNOTHERAPY

Immunotherapy using L-MTP-PE, a liposome-encapsulated immunostimulant derived from a bacterial cell wall, increased survival time to a median of 14.5 months when used after amputation and 4 doses of cisplatin. This drug, known as mifamurtide, is approved in Europe. It has been used in trial situations recently in the USA in people with metastatic OSA; L-MTP-PE may one day be approved in the United States and be available for purchase in the US in the future.

PALLIATIVE THERAPY

Pain Medications

Pain medications alone are generally not very effective at controlling bone pain. Combinations of a nonsteroidal antiinflammatory drug, tramadol, and gabapentin may provide increased comfort for some amount of time. These drugs are often used in conjunction with radiation (RT).

Radiation

One of the most effective palliative treatments is coarse (8Gy per dose) doses of RT given weekly for 3-4 total doses. A recent paper showed good benefits in dogs receiving 2 doses of RT given daily on sequential days. Following RT, improved function can occur in up to 75% of patients. Interestingly, while dogs treated with amputation alone succumb to pulmonary metastasis at a median of 3-5 months, dogs treated only with palliative RT are typically free of pulmonary metastasis at the point at which they succumb to local pain, also at roughly 4 months. Studies have shown that the primary OSA tumor secretes anti-angiogenic factors that are likely involved with the suppression of growth of metastatic lesions. Thus, chemotherapy may not have a role in disease control in dogs treated palliatively with the tumor not removed. Studies assessing the palliative benefits of adjuvant chemotherapy in addition to palliative radiation show varied results, with the majority of papers not showing improved pain control or survival in the dogs that received chemotherapy and RT vs RT alone.

^{153}Samarium-EDTMP (Quadramet$^{TM)}$, a therapeutic radionuclide, is well tolerated and provides pain relief in the majority of dogs treated for appendicular OSA . One advantage of this type of radiation is that it is systemically administered, and thus can treat multiple bone lesions at once. This potential is of more critical relevance in humans, who often have diffuse boney metastasis with cancers of the prostate and breast. However, in the rare

cases of multiple boney sites of OSA in a canine patient, this treatment may be worth seeking. Side effects result from radiation to the bone marrow, and include neutropenia and thrombocytopenia. Combining ^{153}Samarium-EDTMP with carboplatin chemotherapy has been investigated and found to carry a greater risk of significant neutropenia.

Bisphosphonates

Bisphosphonates are widely used in humans with lytic bone disorders. These drugs inhibit osteoclast activity and thus may help decrease boney lysis at the tumor site. Other actions include induction of apoptosis of osteoclasts and potentially malignant osteoblasts; they may also alter the microenvironment within the bone. Interestingly, 3 groups of investigators have shown that bisphosphonates also have direct anti-cancer effects on OSA cell lines in tissue culture. The anticancer effect of bisphosphonates in OSA patients is under investigation. Pamidronate (1-2 mg/kg IV over 2 hrs in 250 mls 0.9% NaCl once every 4 weeks) alone increases comfort in about ¼ of dogs with OSA; pain control was noted for greater than 4 months. When pamidronate was given with palliative radiation and chemotherapy, an increase in pain control was not seen over radiation/chemotherapy alone. Zoledronate (0.1 mg/kg IV over 15 minutes in 60 mls 0.9% NaCl), a next generation bisphosphonate, showed a 50% response in dogs with OSA as a single agent. Findings of a study recently completed at the presenter's institute with zoledronate combined with palliative radiation are very encouraging, with a MST of 250 days. Prognostic factors for success of this therapy are currently being analyzed. Note: oral bisphosphonates are very poorly absorbed in the dog and should not be used.

Metronomic chemotherapy

Metronomic chemotherapy is the administration of small doses of chemotherapy on a very regular and frequent schedule; often daily or every other day. While standard chemotherapy is used to kill malignant cells, the goals of metronomic chemotherapy are to affect the normal endothelial cells that form the lining of newly formed blood vessels, which tumors need for their continued growth. Thus, metronomic chemotherapy is an anti-angiogenic therapy. Additionally, some drugs used for metronomic therapy may suppress T regulatory cells and help the immune system in cancer recognition. One such drug is cyclophosphamide, which has been shown to decrease Tregs, with best effects when used at 15mg/m2 daily. Studies of metronomic chemotherapy in clinical patients are ongoing in both human and veterinary medicine. Anecdotal evidence in dogs with OSA with visible lung metastasis suggests that metronomic chemotherapy may provide stabilization of the size of the nodules for several months. The therapy is also generally well-tolerated. Unfortunately, more recent evidence suggests that metronomic chemotherapy may NOT provide benefit for micrometastatic disease post-amputation and chemotherapy.

Targeted therapy

Toceranib phosphate (Palladia) is a multi-targeted receptor tyrosine kinase (RTK) inhibitor that is active against several members of the split-kinase RTK family including VEGFR, PDGFR and Kit. While approved for mast cell tumors in dogs, off-label use has been frequent amongst veterinary oncologists. Due to the activity against VEGFR and PDGFR, toceranib phosphate may have anti-angiogenic effects and thus may be efficacious against a wide range of tumors. Data collected from veterinary oncologists who used toceranib in dogs with pulmonary metastatic osteosarcoma was recently published. Twenty-three dogs were reported, with 21/23 having been initially treated with amputation and chemotherapy. One (4%) dog had a partial remission, and 10 dogs (43.5%) had stable disease for greater than 6 weeks. The median duration of treatment, and thus response duration, for these 11 dogs was 24 weeks (range 10-42+ weeks).

A recent paper described 126 dogs who received amputation followed by 4 doses of carboplatin. The dogs that were still free of gross metastasis whose owners elected to remain in the study (n=81) then began piroxicam (0.3mg/kg daily)/cyclophosphamide(15mg/m2 daily) with half randomized to also receive toceranib (2.75mg/kg every other day). There was no difference between the two groups, with median disease free interval of 7 months, and median survival of 9 months. While there was no carboplatin chemotherapy only control, these results unfortunately do not appear improved over previous reports of standard chemotherapy alone for management of post-amputation micrometastatic disease.