

Bisphosphonate Treatment for Canine Osteosarcoma

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Purpose

This study was a clinical trial, which evaluated the effect of an oral bisphosphonate as a treatment for appendicular osteosarcoma in dogs on outcome (disease free interval and survival) and palliation (pain/symptom control).

Methods

Dogs presented for evaluation of suspected or confirmed appendicular osteosarcoma were staged with chest radiographs, bloodwork and a bone scan (where available). If no metastases are found they were given all options for treatment; amputation or limb sparing and chemotherapy, palliative radiation or bisphosphonate treatment. If the owner elected bisphosphonate treatment, they were then be enrolled in the study. When applicable, a bone biopsy was obtained from the lesion with the animal under general anesthesia. Alternatively, a biopsy was obtained at the time of amputation or following death, whenever possible. A pain and lameness evaluation was filled out by the owner and a lameness score assigned by the clinician (tables 1 & 2). The degree of palliation was subjectively scored. Radiographs (when obtained and evaluable) of the primary lesion were scored (table 3). Dogs were released to the owner with oral bisphosphonate treatment (see dosages in results below). A CBC and chemistry panel was suggested for all dogs weekly for the first 4 weeks of treatment. Clinical or clinicopathologic toxicities were recorded. At the time of death a complete necropsy was recommended with appropriate tissue sampling. Survival was calculated from the time of treatment initiation to death. The Kaplan Meier Product Limit Method was used to calculate median survival time (SPSS 13.0, Chicago, IL).

Results

A summary of the cases entered, data accrued as well as preliminary results is as follows:

1. Forty two (42) cases have been entered since November of 2001. Case accrual was closed in October, 2005.
2. 8 dogs were initially treated at 10 mg (Fosomax) daily. As no overt toxicity was seen, the remainder of the dogs were treated at 35 mg (per dog) daily.
3. There are 12 castrated males, 9 intact males, 13 spayed females and 8 intact females entered.
4. 7 dogs had preoperative biopsies to confirm osteosarcoma.
5. The median age is 6 years (range 1-9 years)
6. The median time under treatment for all dogs is 83 days (range 13-971 days). The median time of treatment for the low dose group is 118 days (range 35-

- 715 days). The median time of treatment for the high dose group is 83 days (range 13-971 days), the same as the overall group.
7. The median survival for all dogs was 83 days (range 13-971 days). The median survival for the low dose group is 118 days (range 35-715 days). The median survival for the high dose group is 83 days (range 13-971 days), the same as the overall group. The numbers are the same as for the times under treatment.
 8. Tumor sites were; 22 distal radius, 6 proximal humerus, 7 tibia (proximal or distal), 5 distal femur, and one ulna.
 9. The median owner-perceived pain score is 4 out of 14 (range 1-7).
 10. The median veterinary pain assessment score is 6 of 17 (range 3-11).
 11. Most dogs are also being given non steroidal anti-inflammatory medications (NSAID's); the most common drug being Rymadel (carprofen)
 12. One dog had diarrhea, one dog loose stools and one dog constipation. One dog had an elevated blood urea nitrogen (BUN). All other dogs have not shown any clinical signs of toxicity
 13. Although most dogs have had subjective improvement in pain, very few post treatment pain evaluation scores have been returned making objective assessment impossible. (post treatment pain scores pending)
 14. There are 41 dogs that have died and one dog that is still alive at the time of this report (from the high-dose group)
 15. 9 dogs have had necropsies performed (results still pending).

Conclusions:

The drug appears to be well tolerated, even at the higher dose. There is subjective evidence that it is helping with pain relief in the dogs, but this needs to be documented with post treatment pain score evaluations. There may be a slight survival advantage to dogs treated with the drug when compared to untreated dogs; however, this is not statistically significant. There is no significant difference between dogs treated with low dose and those treated with high dose, although the low-dose group has small numbers.

Future Plans:

A pre-proposal was submitted to the Morris Animal Foundation to obtain funding for a trial using bisphosphonates following amputation as adjuvant treatment of osteosarcoma micrometastasis. This proposal was denied. Similar trials are ongoing to evaluate parenteral (intravenous) bisphosphonates as adjuvant therapy for osteosarcoma. If further exploration of the use of oral bisphosphonates is pursued, baseline experimentation will be necessary to evaluate the bioavailability and pharmacokinetics of the drug in dogs. Based on that information, more appropriate dosing regimes could be derived. Trials are ongoing to evaluate the

Table 1**Owner Perceived Pain Score**

Score	Description
Appetite	
0	Normal
1	Slightly Decreased
2	Poor (needs to be coaxed)
3	In appetent
Activity Level	
0	Normal
1	Mildly Decreased (still active on outings)
2	Decreased (participation requires coaxing)
3	Ambulatory Only To Urinate/Defecate
4	Non-Ambulatory
Lameness	
0	No Lameness
1	Weight Bearing But Lamé
2	Periodic Non-Weight-Bearing
3	Complete Non-Weight-Bearing
Analgesic/Adjuvant Use	
0	No *Treatments Utilized
1	Treatments Utilized \leq 8 times/month
2	Treatments Utilized Daily or Every-Other-Day
3	Multiple Daily Treatments
4	Narcotics Used
Total Score	

* "Treatments" refer to non-steroidal antiinflammatories or complimentary therapeutics such as acupuncture, herbal therapy, etc. Owners will list therapies and dosages given when completing the survey.

Table 2*Physical Examination Lameness/Pain Score*

Score	Description
Lameness	
0	None Detectable
1	Intermittent Weight-Bearing
2	Persistent Weight-Bearing
3	Intermittent Non-Weight-Bearing
4	Persistent Non-Weight-Bearing
5	Ambulatory Only With Assistance
6	Nonambulatory
Swelling	
0	None
1	Mild
2	Moderate
3	Severe
Pain on Palpation	
0	None
1	Mild (dog turns head)
2	Moderate (dog pulls limb away)
3	Severe (dog vocalizes, shows aggression)
4	Dog Will Not Allow Examination
Pain on Joint Motion	
0	None
1	Mild (dog turns head)
2	Moderate (dog pulls limb away)
3	Severe (dog vocalizes, shows aggression)
4	Dog Will Not Allow Examination
Total Score	

Table 3

Radiographic Bone Score

Score	Periosteal Response	Cortical Lysis	Sclerosis
0	none	none	None
1	mild	mild	None
2	moderate	moderate	Mild
3	marked	marked	moderate
4	Mild to moderate	Mild to moderate	marked