Samarium Sm 153 lexidronam for the palliative treatment of dogs with primary bone tumors: 35 cases (1999–2005)

Sandra M. Barnard, BVSc; R. Max Zuber, BVSc; Antony S. Moore, BVSc, MVS, DACVIM

Objective—To evaluate survival times and palliative effects associated with the use of samarium Sm 153 lexidronam in dogs with primary bone tumors.

Design—Retrospective case series.

Animals—35 dogs with primary appendicular (n = 32) or axial (3) bone tumors.

Procedures—1 to 4 doses of samarium Sm 153 lexidronam were administered at a rate of 37 MBq/kg (16.8 MBq/lb), IV. Response to treatment, measured by lameness improvement, and survival time were determined.

Results—Of the 32 dogs with appendicular tumors, 20 (63%) had an improvement in the severity of lameness 2 weeks after administration of the first dose of radioactive samarium, 8 (25%) had no change in the severity of lameness, and 4 (12%) had a worsening. Overall median survival time was 100 days, with 3 dogs (8.6%) alive after 1 year. Median survival time for the 32 dogs with appendicular tumors was 93 days, with 3 (9.4%) alive after 1 year. This was not significantly different from the median survival time of 134 days for a historical cohort of 162 dogs with appendicular osteosarcoma that underwent amputation as the only treatment.

Conclusions and Clinical Relevance—Results suggest that samarium Sm 153 lexidronam may be useful in the palliation of pain in dogs with primary bone tumors that are not candidates for curative-intent treatment. (J Am Vet Med Assoc 2007;230:1877–1881)

Currently, the treatment of choice for dogs with primary bone tumors is amputation or limb-sparing surgery with adjunctive chemotherapy. However, concurrent clinical conditions and owner preference may preclude amputation in some patients. In these dogs, medical treatments to alleviate pain, such as administration of NSAIDs, steroids, or opiates, are typically inadequate. External beam radiation therapy has been shown to provide pain relief in 74% to 92% of dogs with skeletal neoplasia, with median times for pain control ranging from 73 to 130 days, but external beam radiation therapy requires specialized equipment, and access may be limited in certain areas.

Samarium 153 is a radioisotope that undergoes both gamma and beta decay. The gamma decay allows the distribution of the isotope to be identified by means of scintigraphy. The beta decay has tissue destructive and therapeutic effects that are limited to tissues within a 2- to 3-mm radius. When samarium 153 is chemically bound to ethylenediaminetetramethylenephosphonic acid, the resulting compound (samarium Sm 153 lexidronam) concentrates in areas of increased osteoblastic activity and binds to exposed hydroxyapatite crystals. This bone-seeking property makes samarium Sm 153 a suitable radiopharmaceutical to consider for targeted radiation therapy of skeletal neoplasia.

Samarium Sm 153 lexidronam has been used in human patients for the palliation of pain associated with various metastatic bone neoplasms, most commonly prostatic and mammary carcinomas. Reported efficacy is between 30% and 95%, with pain relief experienced for up to 11 months. Toxicoses seen in human patients at therapeutic dosages are mild and include reversible leukopenia and thrombocytopenia.

In published reports, samarium Sm 153 lexidronam also appeared to be useful in the palliation of pain associated with primary and metastatic bone tumors in dogs. In regard to pain relief, a variable response rate of 11% to 80% was reported, with 2 cases of complete tumor involution described. As in human patients, the main adverse effect was myelosuppression resulting in thrombocytopenia and leukopenia, which typically resolved within 4 weeks of treatment. The purpose of the study reported here was to evaluate survival times and palliative effects associated with the use of samarium Sm 153 lexidronam in dogs with primary bone tumors in which curative intent treatment was declined.

Criteria for Selection of Cases

Medical records of dogs examined because of bone tumors at the Gladesville Veterinary Hospital between February 1999 and October 2005 were reviewed. Cases

Abbreviation

NSAID Nonsteroidal anti-inflammatory drug
were eligible for inclusion in the present study if the dog had a primary bone tumor and was treated with samarium Sm 153 lexidronam. For the present study, a dog was considered to have a primary bone tumor if it had radiographic evidence of bone lysis and new bone production affecting the metaphyseal area of a long bone at a site known to be a predilection site for primary bone tumors and if signalment of the dog was compatible with reported signalment for dogs with primary bone tumors. Histologic confirmation of the diagnosis was not required for inclusion in the study. Dogs in which amputation or limb-sparing surgery had been performed were excluded.

**Procedures**

Medical records of cases included in the study were reviewed for information related to signalment, samarium Sm 153 lexidronam treatment, concurrent medications for pain relief (ie, NSAIDs, corticosteroids, or tramadol), administration of bisphosphonates, and survival time. In all dogs, samarium Sm 153 lexidronam was administered at a dose of 37 MBq/kg (1.68 MBq/lb), IV. After administration of each dose, dogs were housed in metabolism cages for 3 to 4 days until radiation output over the pelvic region was <10 mR/h, at which time dogs were discharged from the hospital.

A CBC was performed 2 weeks after administration of each dose of samarium. One to 4 doses of samarium Sm 153 lexidronam were given. Multiple doses were given on the basis of each individual dog’s response to the previous treatment and the owner’s financial commitment.

When possible, toxicoses were graded on the basis of criteria established by the Veterinary Cooperative Oncology Group. Toxicoses were recorded 2 weeks after the first dose of samarium Sm 153 lexidronam and included neutropenia, thrombocytopenia, diarrhea, and pressure sores.

Response to treatment was assessed only in dogs with appendicular tumors and only after administration of the first dose of radioactive samarium. For this assessment, the referring veterinarian or owner was asked to indicate whether severity of lameness 2 weeks after administration of the first dose of radioactive samarium was worse, unchanged, or improved.

**Statistical analysis**—The Pearson $\chi^2$ or Fisher exact test was used to determine whether response to treatment (ie, lameness worse vs unchanged or improved) was significantly associated with sex (sexually intact male vs neutered male vs sexually intact female vs neutered female), use of bisphosphonates (yes vs no), use of NSAIDs (yes vs no), tumor location (forelimb vs hind limb), posttreatment swelling (yes vs no), breed (Rottweiler vs any other breed), number of treatments, histologic confirmation of neoplasia (yes vs no), and response to treatment (ie, lameness worse vs unchanged or improved). Cox regression was used to determine whether these categorical variables or various continuous variables (ie, time from diagnosis to treatment, age, and body weight) were associated with survival time. Variables found to be significant at the level of $P < 0.05$ in univariate analyses were entered into a Cox forward logistic regression model to determine whether they retained significance ($P < 0.05$) under multivariate analysis.

The Kaplan-Meier method and Cox regression method were also used to compare survival times for the 32 dogs with appendicular tumors in the present study with survival times for a historical control population of 162 dogs treated by means of amputation alone. Standard software was used for all analyses.

**Results**

Thirty-five dogs met the criteria for inclusion in the study. There were 15 males (7 castrated) and 20 females (15 spayed). Median age was 8 years (range, 2 to 15 years), and median body weight was 49 kg (108 lb; range, 16.5 to 71 kg [36 to 156 lb]). There were 11 Rottweilers, 3 Rottweiler crossbreds, 6 Great Danes, 5 German Shepherd Dogs, 2 Labrador Retriever crossbreds, 2 Irish Wolfhounds, 1 Bullmastiff, 1 Bearded Collie, 1 American Staffordshire Terrier crossbred, 1 Dalmatian, 1 German Shorthaired Pointer, and 1 Australian Cattle Dog crossbred.

Thirty-two dogs had appendicular tumors and 3 had axial tumors. Sites of primary tumor involvement included proximal aspect of the humerus (n = 10), distal aspect of the radius (8), distal aspect of the ulna (2), scapula (3), proximal aspect of the tibia (2), distal aspect of the tibia (6), distal aspect of the femur (1), mandible (1), and vertebral column (2). In 21 dogs (19 with appendicular tumors and 2 axial tumors), the diagnosis was confirmed histologically. Of these, 19 had an osteosarcoma, 1 had a fibrosarcoma, and 1 had a chondrosarcoma. In the remaining 14 dogs, a presumptive diagnosis of a primary bone tumor had been made. Right lateral, left lateral, and ventrodorsal radiographic projections of the thorax had been obtained in 18 dogs, and...
and none of the 18 had radiographic evidence of pulmonary metastasis at the time of diagnosis.

Median time from diagnosis to administration of the initial dose of radioactive samarium was 14 days (range, 1 to 53 days). A total of 59 doses of samarium Sm 153 lexidronam were given. Sixteen dogs received 1 dose, 13 dogs received 2 doses, 2 dogs received 3 doses, and 4 dogs received 4 doses. Median time between administration of the first and second doses was 49 days (range, 35 to 112 days), median time between administration of the second and third doses was 58 days (range, 36 to 532 days), and median time between administration of the third and fourth doses was 87 days (range, 63 to 109 days).

Thirty-four dogs received concurrent medications for pain relief, either NSAIDs (n = 32) or corticosteroids (2). Of the 32 dogs that received NSAIDs, 7 also received corticosteroids, but not concurrently. Seven dogs were treated concurrently with the bisphosphonate alendronate at a dosage of 70 mg, PO, once weekly. Five dogs were treated with tramadol (1 to 4 mg/kg [0.45 to 1.8 mg/lb], PO, q 12 h or q 24 h); 3 received tramadol concurrently with NSAIDs and 2 received tramadol concurrently with corticosteroids.

Of the 32 dogs with appendicular tumors, 20 (63%) reportedly had subjective evidence of an improvement in the severity of lameness 2 weeks after administration of the first dose of radioactive samarium. Eight (25%) dogs had no change in the severity of lameness 2 weeks after treatment, and lameness was worse in the remaining 4 (12%) dogs.

At the time of the present study, all dogs had died or been euthanatized. Twenty-four dogs had been euthanatized because of signs of ongoing or recurrent pain associated with the primary tumor (23 with appendicular tumors and 1 with a tumor of the vertebral column). One dog was euthanatized because of dyspnea related to metastases (appendicular tumor). Seven dogs died or were euthanatized for reasons unrelated to the bone tumor or radioactive samarium treatment (5 with appendicular tumors and 2 with axial tumors). Two dogs died of unknown causes (both with appendicular tumors). Owners of 1 dog elected to have the limb amputated 261 days after administration of the first dose of radioactive samarium; a total of 3 doses of radioactive samarium had been administered in this dog. There was no radiographic evidence of pulmonary metastases at the time of amputation; the dog died within 5 hours after surgery.

Overall median survival time was 100 days (range, 4 to 735 days), with a 1-year survival rate of 8.6% (3/35; Figure 1). Median survival time for the 32 dogs with appendicular tumors was 93 days (range, 4 to 735 days), with a 1-year survival rate of 9.4% (3/32). Survival time for dogs with appendicular tumors was not significantly (P = 0.316) different from survival time (median, 134 days) for the historical control group of 162 dogs with appendicular osteosarcoma treated by means of amputation alone (Figure 2). For the 32 dogs with appendicular tumors, only number of treatments (P = 0.002) and response to treatment (ie, lameness worse vs unchanged or improved; P < 0.001) were found to be significantly associated with survival time. Median survival time for the 15 dogs with appendicular tumors that received a single dose of radioactive samarium was 49 days (range, 4 to 381 days), with 1 dog alive after 1 year; median survival time for the 11 dogs that received 2 doses was 118 days (range, 65 to 359 days), with none alive after 1 year; median survival time for the 2 dogs that received 3 doses was 261 days (261 and 735 days), with 1 dog alive after 1 year; and median survival time for the 4 dogs that received 4 doses was 220 days (range, 154 to 430 days), with 1 dog alive after 1 year.

Median survival time for the 4 dogs with appendicular tumors in which severity of lameness 2 weeks after the first dose of radioactive samarium was reportedly worse was 15 days (range, 4 to 49), with none of the 4 alive 1 year after treatment. For the remaining 28 dogs in which lameness was unchanged or improved, median survival time was 118 days (range, 24 to 735 days), with 3 dogs alive after 1 year. Median survival...
time for the 8 dogs in which severity of lameness was unchanged was significantly ($P = 0.017$) different from median survival time for dogs in which lameness was worse, but was not significantly ($P = 0.23$) different from median survival time for dogs in which lameness was improved.

For the 32 dogs with appendicular tumors, sex was the only factor found to be significantly ($P = 0.03$) associated with response to treatment (ie, lameness worsened vs unchanged or improved). Castrated male dogs were significantly less likely to respond to treatment than were other dogs. Median survival time for the 21 dogs that had histologic confirmation of disease was not significantly ($P = 0.393$) different from that for the 14 dogs that did not.

Toxicoses—Results of a CBC performed 2 weeks after administration of the first dose of radioactive samarium were available for 30 of the 35 dogs. Results were not available for 3 dogs, and in 2 dogs, only qualitative comments regarding CBC results were recorded in the medical record. Sixteen of the 35 dogs had neutropenia, with neutropenia classified as grade 1 in 13 dogs, grade 2 in 1 dog, and grade 3 in 2 dogs. Twenty-seven dogs had thrombocytopenia, with thrombocytopenia classified as grade 1 in 4 dogs, grade 2 in 10 dogs, grade 3 in 8 dogs, and grade 4 in 5 dogs. None of the dogs had clinical evidence of hemorrhage, and no changes to subsequent doses were made. One dog was hospitalized because of septicemia 2 weeks after receiving a dose of radioactive samarium. The dog had grade 1 neutropenia and grade 4 thrombocytopenia and responded to treatment with fluids and antimicrobials.

Eleven dogs developed pressure sores associated with confinement following administration of radioactive samarium, with 4 dogs having grade 1 pressure sores (no treatment required) and 7 dogs having grade 2 pressure sores (antimicrobial treatment required).

Two dogs developed diarrhea following administration of radioactive samarium, with 1 having grade 1 diarrhea and the other having grade 2 diarrhea. One dog with recurring bacterial cystitis prior to treatment had a recurrence of cystitis after treatment, and 2 dogs developed respiratory tract infections that responded to treatment with antimicrobials.

Twenty dogs were treated with antimicrobials after being treated with radioactive samarium, including 5 dogs that received antimicrobials prophylactically because of neutropenia. Twenty-two dogs had swelling associated with the tumor site following treatment that was thought to be an inflammatory response to treatment. In 1 dog, lameness was substantially worse 1 week after administration of the first dose of radioactive samarium but improved thereafter.

Discussion

Results of the present study suggested that samarium Sm 153 lexidronam may be useful in the palliation of pain in dogs with primary bone tumors. A decrease in the severity of lameness was reported in 23 of the 32 (73%) dogs with appendicular tumors, which compares favorably with response rates reported previously and with response rates reported for palliative external beam radiation therapy. In addition, survival times were similar to survival times for a historical cohort of dogs treated by means of amputation alone.

The duration of response could not be accurately determined in the present study. Therefore, survival times were analyzed, as we reasoned that most dogs would be euthanatized when pain was no longer adequately controlled. Although survival times for dogs in the present study were not significantly different from survival times for a cohort of dogs treated by means of amputation alone, radioactive samarium should not be considered as a substitution for amputation because amputation is 100% effective in palliating pain. In addition, our finding that survival times for dogs in the present study were not significantly different from survival times for the historical cohort should be interpreted with caution because although all dogs in the historical cohort were confirmed to have osteosarcoma on the basis of histologic examination, only 19 dogs in the present study were confirmed histologically to have osteosarcoma. In addition, dogs in the historical cohort were treated 11 to 27 years prior to the present study, and access to adjunctive treatments such as pain-relief medications would likely have been different.

A potential limitation of the present study is that histologic confirmation of the diagnosis was obtained in only 21 of the 35 (60%) dogs. However, this is similar to the percentage of dogs with a confirmed diagnosis in studies of the palliative effects of external beam radiation. Also, in the present study, we did not find any significant difference in survival times or response rate between dogs in which the diagnosis was confirmed histologically and dogs in which it was not.

Nine dogs (26%) in the present study were euthanatized or died for reasons unrelated to the bone tumor or radioactive samarium treatment or for unknown reasons. This high percentage likely reflects the nature of patients included in the study. In general, dogs treated with radioactive samarium were poor candidates for surgery because of concurrent diseases, such as renal failure, congestive heart failure, lymphoma, and immune-mediated hemolytic anemia. Dogs were not censored in the survival analysis because the duration of response to treatment with radioactive samarium could not be accurately determined. Because necropsies were not performed, the tumor may have contributed to the death of some of these dogs, even if pain associated with the primary tumor was controlled. This should be taken into account when comparing results of the present study with results of studies in which censoring was used.

Previous reports described 2 dogs with tumor involution following radioactive samarium treatment. Tumor involution was not observed in the present study; however, only 1 dog was confirmed to have been euthanatized because of pulmonary metastatic disease, and this dog was not euthanatized until 735 days after the first dose of radioactive samarium was administered. This is consistent with findings of another study in which development of metastases was seemingly postponed after treatment with radioactive samarium. Importantly, however, dogs in the present study were not consistently screened for pulmonary metastases.

Although number of treatments was significantly associated with survival time in the present study,
we believe that this simply reflects the fact that dogs that lived longer were able to receive more treatments. There was possibly also a bias against treating those dogs that did not respond after the first dose of radioactive samarium. If no improvement in lameness occurred, owners were informed that a second dose was unlikely to be of benefit. Owner financial constraints also affected the number of treatments given. On the other hand, individual dogs subjectively appeared to continue to respond to repeated treatments with radioactive samarium. Recent discussion about the use of external beam radiation therapy suggests that the benefit of intermittent treatments may be to extend response time with minimal cumulative effects of radiotherapy.5

As expected with a retrospective study, there were inconsistencies in the data. Not all cases had histologic confirmation, but this was not significantly associated with survival time or response to treatment. Unfortunately, it was not possible to obtain pretreatment radiographs for all dogs. Thus, we could not determine whether radiographic changes were associated with treatment response or survival time. It has been shown previously that tumors that extend beyond the periosteum are associated with a poorer response8,9 and that tumors of the osteoblastic-sclerotic type should respond more readily.10 Although one of the authors (RMZ) had a subjective clinical impression that dogs with tumors that had a large soft tissue component were less likely to respond, this could not be examined because of a lack of objective data in the records.

Pressure sores have not been reported previously as an adverse effect of radioactive samarium treatment. In this instance, development of pressure sores was likely related to statutory regulations regarding radiation safety that mandated caging of dogs following treatment, which likely resulted in longer hospitalization time than in previous studies. Dogs in the present study were housed in metabolism cages for 4 days after receiving radioactive samarium.

Myelosuppression was the most common toxicosis in the present study, although the degree to which myelosuppression could be attributed to radioactive samarium treatment could not be assessed because results of pretreatment CBCs were not available. Toxicoses in the present study were similar to those reported previously, although 1 dog in the present study did have to be hospitalized because of sepsis 2 weeks after administration of the first dose. Thrombocytopenia was subclinical in all cases, and none of the dogs died because of the treatment. Thrombocytopenia was the main toxicosis seen in a pilot study of low-dose whole body radiotherapy13 and, in the present study, may have been a consequence of nonspecific bone targeting by radioactive samarium. One dog was reported to have had a transient increase in the severity of lameness after treatment; a similar response has been reported in human patients.7

When external beam radiation therapy is used for palliation of bone tumors in dogs, chemotherapeutic drugs are sometimes administered concurrently to increase cytotoxic effects on the primary tumor or decrease metastasis.5 Myelosuppression seen in dogs in the present study was of a similar magnitude to that seen following administration of some chemotherapeutic drugs used for the adjuvant treatment of osteosarcoma. Thus, in these dogs, administration of adjuvant chemotherapeutic drugs would have to have been delayed.

References