Clinical and Clinicopathologic Response of Canine Bone Tumor Patients to Treatment with Samarium-153-EDTMP

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Forty dogs with spontaneous skeletal neoplasia were treated with ^{153}Sm-EDTMP (ethylenediaminetetramethylene phosphonic acid). Both primary and metastatic lesions were treated. Two treatment regimes, a single (37 MBq (1.0 mCi)/kg dose or two 37 MBq (1.0 mCi)/kg doses separated by 1 wk) were tested. Response to treatment was varied. Large lesions with minimal tumor bone formation responded poorly, while primary lesions with substantial ossification usually exhibited a transient response. Small lesions with minimal lysis, metastatic lesions, and axial skeleton lesions generally responded well. The major adverse side effects of treatment were platelet and white blood cell count depression below baseline values for up to 4 wk ($p < 0.05$). Minor depression of packed cell volume and transient elevation of serum alkaline phosphatase were also noted ($p < 0.05$). No significant differences ($p > 0.05$) between the two treatment groups, either in treatment effect or undesirable side effects, were detected.

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Advances in therapy for primary tumors have resulted in a improved probability of local control for many soft-tissue and osseous neoplasms (*1,2*). Unfortunately, preservation of function in cases of skeletal neoplasia is often difficult to achieve when curative surgical and/or radiation therapy is employed. Furthermore, the majority of human skeletal neoplasias are metastatic in origin with multiple bone involvement (*3, 4*). This often precludes surgical resection or curative radiotherapy of the lesions, especially where the spine is involved. Except for a few isolated instances, such as testicular neoplasia, there have been few recent new developments in the control of such metastatic lesions. Since skeletal metastases are responsible for much of the morbidity and mortality associated with cancer, significant improvements in effective therapy of these lesions represent major advances in cancer management.

Treatment of metastatic neoplasia often consists of combining modalities such as external beam radiation therapy and chemotherapy (*5*). Radiation teletherapy is employed to control or palliate skeletal metastases (*6,7*). Chemotherapy is then used to control metastatic lesions in the soft tissues and to potentiate the effect of the radiation on the irradiated lesions. However, the usefulness of external beam irradiation of skeletal metastasis is severely limited due to the injuries that therapeutic doses of ionizing radiation incur in normal tissues included in the radiation field and the difficulty in treating some areas without injuring adjacent, vital, radiation-sensitive tissues (*8–10*).

Recently, the use of biochemically targeted beta-particle-emitting radioisotopes to selectively deliver therapeutic doses of ionizing radiation to neoplastic lesions has been under investigation (*11–15*). Biochemically targeted radioisotope therapy has appeal for the the treatment of metastasis because of the marked reduction in radiation dosage to the normal tissues surrounding the lesion. This reduction results from localization of the radiation source within the lesion, the short range of the beta particles in tissue and the characteristic Bragg-Grey energy deposition curve of beta particles. Thus, it is theoretically possible that if the lesion to non-lesion isotope deposition ratio were high enough, all neoplastic cells within a lesion could be lethally irradiated without significant dosage to more than a few millimeters of the adjacent normal tissue.

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Deposition of radioactivity in normal organs and tissues distant to the neoplasm or in portions of the organ of origin not involved with the tumor must be minimal for such a biochemically targeted radiopharmaceutical to be useful. Since the metabolic activity of both tumor and normal tissues is very similar some irradiation of the unaffected organ tissues will invariably result. However, greatly enhanced metabolic rates in and around the tumor can result in increased deposition of radiopharmaceutical in the tumor. This results in lesion to normal tissue ratios which may permit irradiation of the tumor to therapeutic levels without exceeding the tolerance of the normal tissues (*16,17*). The tissue of critical interest for bone neoplasia is the bone marrow. Any agent localizing in the skeleton as a whole must do so at a level below that which will result in permanent damage to the marrow.

Samarium-153 (^{153}Sm) is a medium-energy beta-particle-emitting ($E_{\beta max}$ = 0.80 MeV, $T_{½}$ = 46.8 hr) radioisotope, which also emits a 28% abundant, 0.103 MeV gamma photon. Experiments in our laboratory using normal adult beagles have demonstrated that significant but transient leukocyte and platelet depression is associated with the administration of single or multiple ^{153}Sm-EDTMP (ethylenediaminetetramethylene phosphonic acid) doses calculated to deliver 40 Gy to neoplastic bone lesions (*16–18*). These animals did not exhibit clinical signs associated with the reduced leukocyte and platelet counts and the bone marrow recovered without treatment. The only observed clinical or clinicopathologic abnormality attributable to the radioisotope was a slight rise in serum alkaline phosphatase levels during the first week after administration. This report deals with both the clinical pathologic findings and the tumor response observed in two groups of patient dogs with naturally occurring skeletal neoplastic disease.

MATERIALS AND METHODS

Forty dogs with a variety of skeletal neoplasias were treated with ^{153}Sm-EDTMP (Table 1). The dogs (21 male and 19 female) ranged in age from 18 mo to 15 yr. Osteogenic sarcoma was the most common tumor type represented (30), with the remainder being chondrosarcomas (2), fibrosarcomas (4), undifferentiated sarcoma (2), and soft-tissue neoplasias either extending directly into or metastatic to bone (2). The distal radius was the most common site of occurrence (11), but a variety of other lesion sites were represented (Table 1), including eight in the spine and skull. Twenty dogs were administered a single intravenous injection of 37 MBq (1.0 mCi/kg) ^{153}Sm-EDTMP and 20 received two injections of 37 MBq (1.0 mCi/kg) one week apart. Each dog was evaluated physically, clinicopathologically, and radiographically prior to admission to the treatment protocol. Clinicopathologic parameters recorded were serum biochemistries (Na, K, Na/K ratio, P, Cl, Ca, glucose, total protein, albumin, globulin, A/G ratio, blood urea nitrogen (BUN), ALT, and ALP), complete blood count (CBC) packed cell volume (PCV), WBC count, differential WBC count, absolute platelet count), bone marrow biopsy and urinalysis. Radiographic studies included plain radiographs of the lesion and the thorax. The size, appearance, lesion location, and degree of lameness or disability caused by the tumor were recorded on the physical examination along with any other physical abnormalities. Bone marrow biopsies, lesion biopsies, lesion and nuclear medicine bone scans using technetium-99m-MDP (^{99m}Tc-MDP) were also obtained prior to administration of ^{153}Sm-EDTMP. Forty-eight hours after administration of ^{153}Sm-EDTMP, bone scans using the 103-keV, 28% abundant gamma photon of the ^{153}Sm were obtained.

Weekly CBC and platelet counts, serum biochemistries, and urinalyses were performed for the first four weeks after treatment. If severe leukopenia (<2,500 cells/mm^3) occurred, amoxicillin was administered prophylactically. Four weeks after treatment, the entire preliminary workup protocol was repeated, and the dog was released to its owner if response to treatment had occurred. Reevaluation of these animals was then scheduled at 2, 3, 6, 9, 12, 18, and 24 mo after treatment. Some dogs died or were euthanized at the owners request during the first 4 wk because of little or no response to the treatment. These animals were considered non-responders. Dogs which demonstrated an initial treatment response but eventually died of their disease were considered transient responders with a positive palliative effect. Animals which survived for 24 mo following ^{153}Sm-EDTMP treatment without evidence of disease were considered to be cured of their disease.

The data acquired during the week before and the first five weeks after initiation of treatment were analyzed using Wilcoxon's Signed Rank Test for changes from baseline within the individual groups for the diseased dogs. Significance was recognized at a value of $p \leq 0.05$ for this test. Response differences between the two dose groups of the experiment were evaluated using Wilcoxon's Rank Sum Test. Significance

TABLE 1
Tumor Type, Location, and Survial in 40 Dogs Treated with ^{153}Sm-ETMP

Tumor type	Site	No. animals	Mean age (yr)	Mean survival (mo)
Carcinoma	Axial skeleton	2	10	3
Nonosseous sarcoma	Axial skeleton	1	14	15
Osteosarcoma	Axial skeleton	8	10	12
Nonosseous sarcoma	Appendicular skeleton	7	8	10
Osteosarcoma	Radius or ulna	9	7	7
Osteosarcoma	Humerus	4	7	5
Osteosarcoma	Tibia	3	9	13
Osteosarcoma	Femur	4	8	7

for these comparisons was also recognized at values of $p \leq 0.05$. Since the use of an untreated diseased control dog groups was not felt to be justifiable, the clinicopathologic responses of the diseased dogs were compared to a control group of untreated normal dogs and a group of normal treated dogs given a single 1.0 mCi/kg (37 MBq) intravenous dose of ^{153}Sm-EDTMP (*18*). These dogs were housed under the same conditions as the diseased dogs. The Wilcoxon Rank Sum test was used to evaluate these comparisons. Significance was recognized at values of $p \leq 0.05$.

RESULTS

Response to treatment was variable (Table 2). Currently seven dogs are considered disease free. Only dogs living more than 11 mo after treatment and either alive without known neoplastic disease or dead from other causes with no post mortem evidence of neoplastic disease are included. The mean survival time of this group is currently 27 mo. Of these, four dogs which initially responded to ^{153}Sm-EDTMP treatment subsequently had amputations or other anti-neoplastic treatments performed following tumor recrudescence. Two dogs in this group are still alive and considered cured of their disease without further treatment after more than three years. One, the dog with a chondrosarcoma of the humerus, has had complete involution of her lesions and has a radiographically normal humerus at this time (Fig. 1). The other, a dog with a mandibular osteosarcoma, had such severe destruction of the bone that complete remodeling was not possible but complete involution of the lesion is evident radiographically (Fig. 2). All of the dogs (3) in which a complete and prolonged response was achieved without the performance of additional therapeutic procedures were in the single dose group.

TABLE 2
Response of 40 Dogs with Bone Tumors to Treatment with ^{153}Sm-EDTMP

Response	Total	Alive	Amputation	×Survival (mo)	Range (mo)
Disease free*	7	4	2	26.9	11–45
Partial response†	25	0	12	5.2	1–16
No response‡	8	0	2	0.7	0.5–1

* Dogs living more than 11 mo post-treatment and alive and disease free or died from unrelated causes with no necropsy evidence of disease.

† Initial functional and radiographic improvement followed by regrowth of tumor or metastatic disease. Euthanasia recommended if amputation or retreatment failed.

‡ No initial response of primary tumor, euthanasia recommended, or died of complications of disease.

Twenty-five dogs had a partial response to ^{153}Sm-EDTMP treatment. In these dogs, there was an initial treatment response as evidenced by functional improvement and radiographic involution of the lesion (Fig. 3), but each animal subsequently suffered regrowth of the tumor and either died from their disease or is alive with known disease. Several of these dogs (6) have had amputations, chemotherapy, or both performed without control of their disease following recrudescence. The mean survival time in this group is 5.2 mo (range of 1–16 mo).

Eight dogs failed to respond to the ^{153}Sm-EDTMP treatment. Most of these animals were presented in poor condition with far advanced neoplastic disease. Two were functionally paralyzed due to spinal involvement with spinal cord compression. Functional impairment was advanced in all of the remaining seven, such that the affected limb was completely non-weight bear-

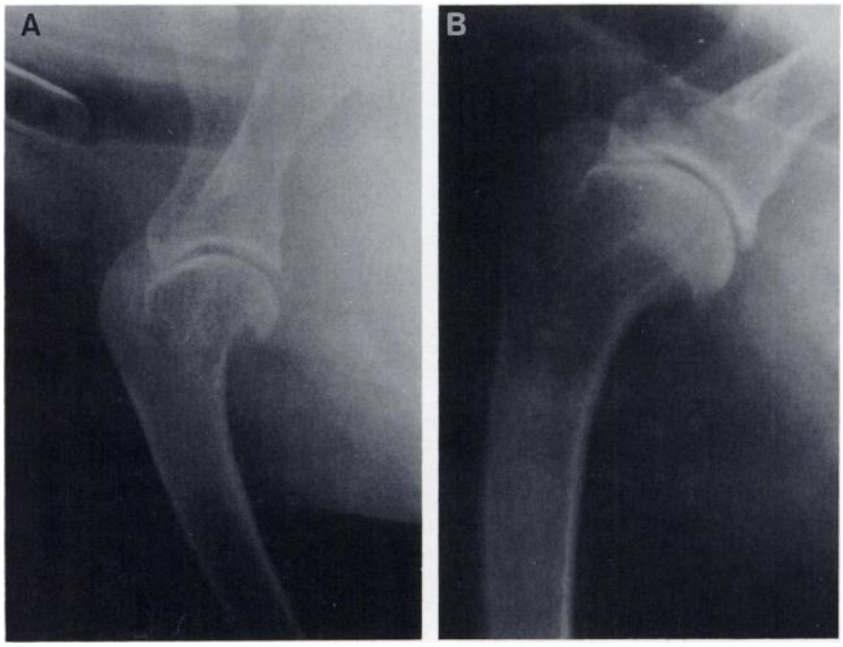

FIGURE 1
Radiographs from a dog with a chondrosarcoma of the proximal humerus. (A) The original lesion before treatment. Diffuse punctate lysis of the proximal humeral shaft is evident. (B) the same humerus 27 mo after treatment. Note the complete repair of the original lesion.

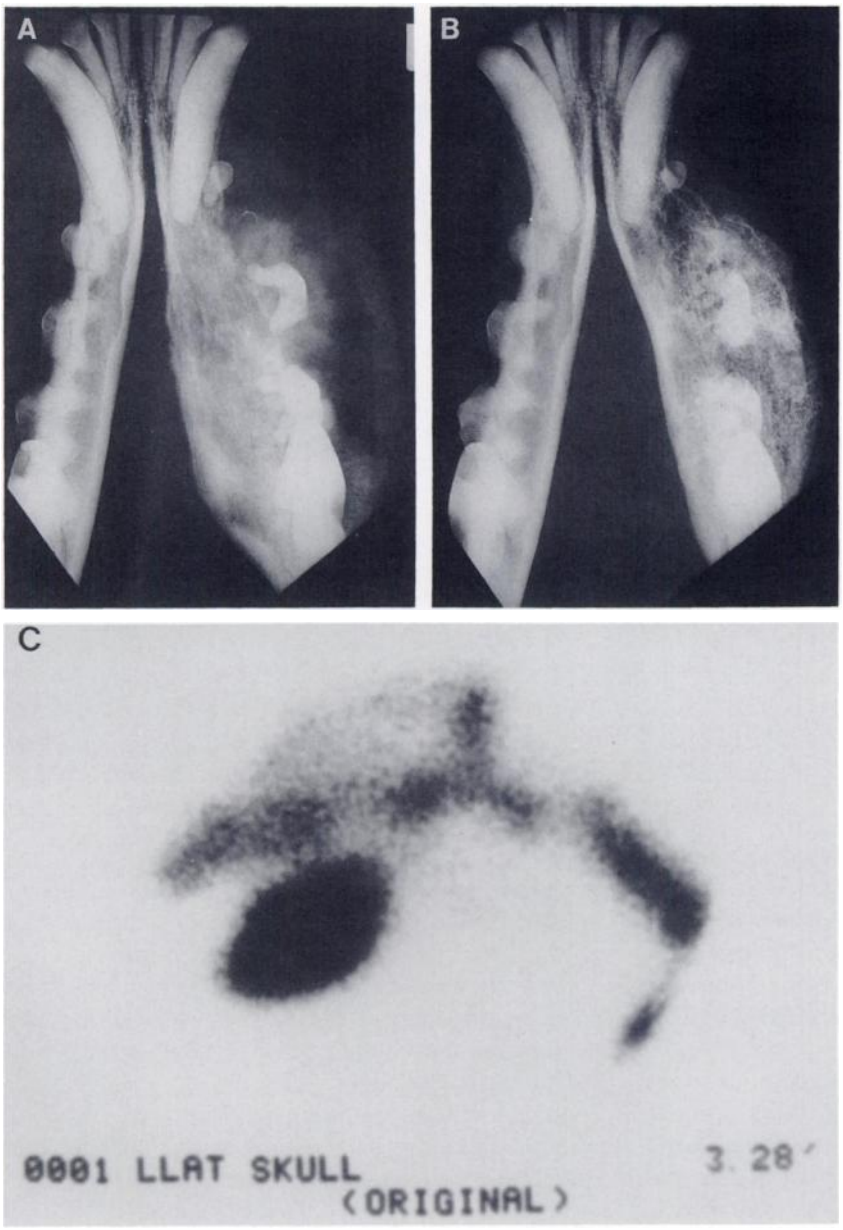

FIGURE 2
Radiographs from a dog with an osteosarcoma of the body of the mandible. (A) The original lesion before treatment showing extensive destruction of the body of the mandible with expansion of the cortex and exuberant periosteal reaction of a very aggressive character. (B) The same mandible three years after treatment with ^{153}Sm-EDTMP. The lesion is completely quiescent and has remained static since treatment. No distant metastasis have developed. (C) Lateral scintiscan of the original lesion indicating intense diffuse uptake of the radionuclide in the lesion.

ing and had radiographic evidence of pathologic fracture. Dogs with lesions of this type are now no longer being considered for treatment with ^{153}Sm-EDTMP because of the poor response rate and humane considerations related to management of large painful tumors without reasonable expectation of therapeutic effect from the treatment method employed.

Metastatic lesions were identified in some of the dogs, including one dog which had widespread skeletal metastatic disease from an epithelial carcinoma of the lung. Although survival time was short in this animal, there was definite evidence of pain palliation (decreased stiffness, improved mobility, and increased appetite) following treatment. In the dogs with metastatic lesions, bone scan evaluations determining the radioisotope uptake pattern indicated a uniformly intense uptake of the radioisotope within the entire lesion (Fig. 4).

No statistically significant increase in treatment effect ($p > 0.05$) was observed for the animals which received the two treatment protocols. The medical records of the animals in the two groups did not indicate any difference in the degree of pain palliation. Palliation was judged on the basis of improved ambulation and was neither increased in degree nor prolonged in duration in the two treatment groups over that in the single treatment group. Relative radioisotope uptake in the lesion and normal bone was not significantly different between the first and second injections ($p > 0.05$) on the basis of quantitative evaluation of lesion to normal bone uptake ratios determined from gamma camera scans.

The pattern of uptake of ^{99m}Tc-MDP in osseous lesions reflected that of the ^{153}Sm-EDTMP without visibly detectable differences (Fig. 5). Therefore, the

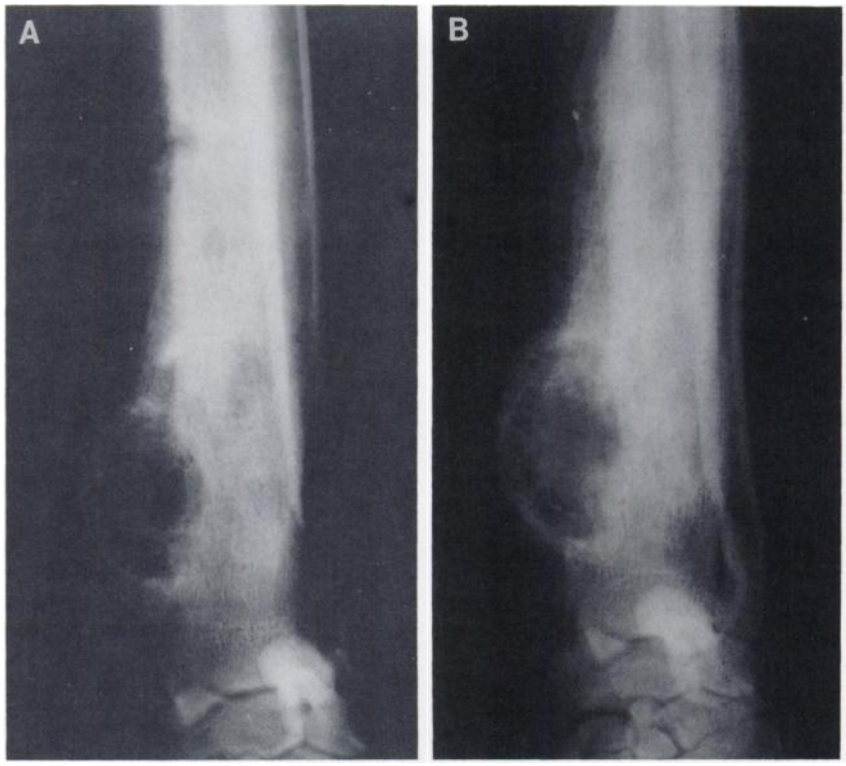

FIGURE 3
Radiographic evidence of reduced tumor activity following treatment with ^{153}Sm-EDTMP. (A) Radiograph of the distal foreleg of a dog with medullary osteosarcoma prior to treatment. Note the highly active periosteal reaction and indistinct margination of the areas of lysis. (B) Radiograph of the same lesion 3 mo after treatment with ^{153}Sm-EDTMP. Note the reduction in the activity aggressiveness of the periosteal reaction and the more distinct margination of the lytic zones.

^{99m}Tc bone scan is an accurate predictor of the probable localization of ^{153}Sm-EDTMP treatment and potentially of the expected efficacy of such treatments. Patient dogs with ^{99m}Tc-MDP studies that did not indicate good localization of the radioisotope in the lesion of interest did not benefit measurably from ^{153}Sm-EDTMP treatment.

Clinicopathologic evaluation of these dogs following intravenous administration of 37-74 MBq (1–2 mCi/kg) of ^{153}Sm-EDTMP indicated occurrence of bone marrow suppression parallel to that observed in the normal beagles (16). Significant reduction in circulating leukocytes and thrombocytes occurred Weeks 1 through 4 after a single injection and Weeks 1 through 5 in dogs receiving two injections of the drug ($p < 0.05$) (Figs. 6 and 7). Although the leukocyte and platelet counts were markedly decreased in some dogs (<2,500 cells/mm^3 and <20,000 cells/mm^3, respectively), none showed any physical evidence of infection in thrombocytopenia and none developed anemia suggestive of the presence of chronic internal hemorrhage. Cell counts were depressed longer in the dogs which received two injections than in those which received a single injection, but the absolute cell counts during the period of depression did not significantly ($p > 0.05$) differ between the two groups except for platelets during Week 2 ($p < 0.05$) (Figs. 6 and 7). Thus, multiple therapeutic level doses were tolerated by the patient animals without increased risk of bone marrow ablation.

The PCV demonstrated a statistically significant ($p < 0.05$) decline from the pretreatment baseline values, however the values did not fall below the lower limit of the normal range (32–55) for the University of Missouri—Columbia Veterinary Teaching Hospital labo-

FIGURE 4
Samarium-153-EDTMP scintiscan of a dog with widespread skeletal metastatic disease from a primary pulmonary carcinoma. The scan indicates that even the relatively large metastatic lesions in this animal's skeleton concentrate the ^{153}Sm-EDTMP quite well. Following treatment this dog's ability and willingness to ambulate improved markedly. She succumbed to her soft-tissue metastatic disease within a few weeks but continued to have apparent relief from skeletal pain until death.

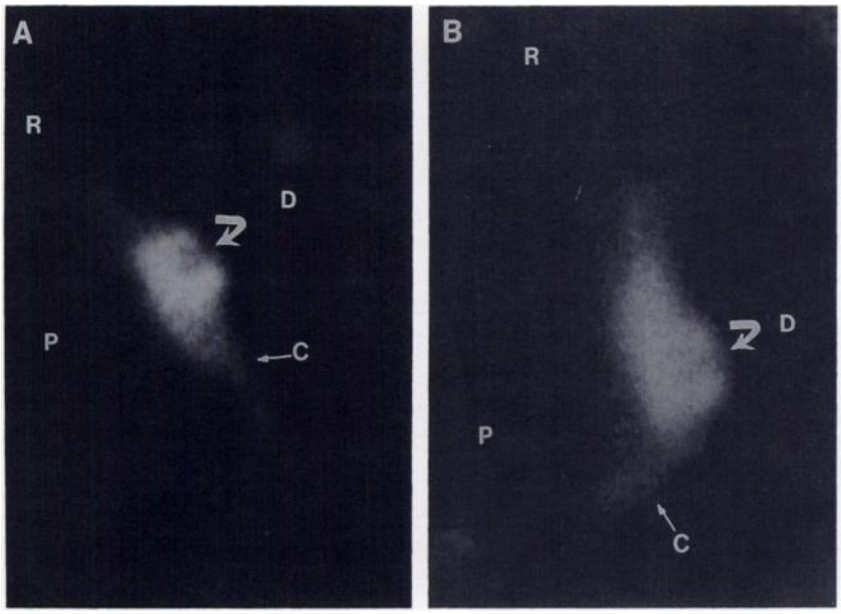

FIGURE 5
Comparison of ^{99m}Tc-MDP and ^{153}Sm-EDTMP scintigraphic images of the initial lesion in the distal radius from the animal in Figure 3, (R = proximal radius, C = carpus, D = dorsal, and P = palmar). (A) Technetium-99m-MDP scintigraphic image. This image was made ~1 hr after injection of the ^{99m}Tc-MDP. (B) Samarium-153-EDTMP scintigraphic image of the initial lesion from the same animal obtained ~24 hr after injection of the radiopharmaceutical. The two images are virtually identical and both indicate the presence of an area of decreased uptake (curved arrow) in the center of the lesion. Such area of decreased uptake generally heralded a transient response as was the case in this animal.

ratory (Fig. 8). This reduction was prolonged by one week in the dogs receiving two injections. However, there was no significant difference ($p > 0.05$) in the responses of the two treatment groups at any of the evaluation points when the two were compared with each other.

As in the normal dog studies, the leukocytes and platelets returned to normal levels ~4 wk after the last injection (Figs. 6 and 7). Recovery of the PCV was also evident at this time (Fig. 8). In no case has there been a subsequent decline in marrow activity detected at the follow-up examinations performed at up to 2 yr post-treatment. The bone marrow is apparently able to respond to the suppression of blood cell precursors induced by ^{153}Sm irradiation and does not become secondarily exhausted at a later time.

Comparison of the responses for hematologic and enzymatic parameters in the group of diseased dogs receiving a single dose of 1.0 mCi/kg to those in normal beagles administered a single 1.0 mCi/kg dose

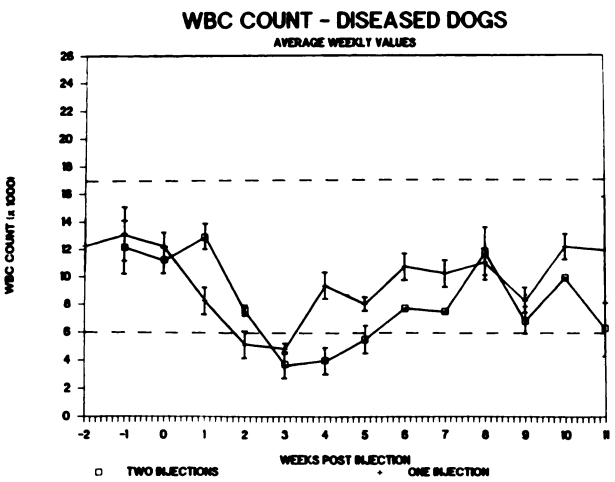

FIGURE 6
White blood cell counts in dogs with various skeletal neoplasms before and for 10 wk after treatment with ^{153}Sm-EDTMP. Graphs are for two treatment groups, 1 mCi (37 MBq)/kg once and 1 mCi (37 MBq)/kg twice with 1 wk between the two injections. The graphs indicate the recovery delay imposed by the second injection and the return to normal levels (6,000–17,000 cells/microliter) at ~4 wk after the last injection of radiopharmaceutical. None of the animals exhibited any clinical evidence of disease susceptibility during the time that counts were reduced.

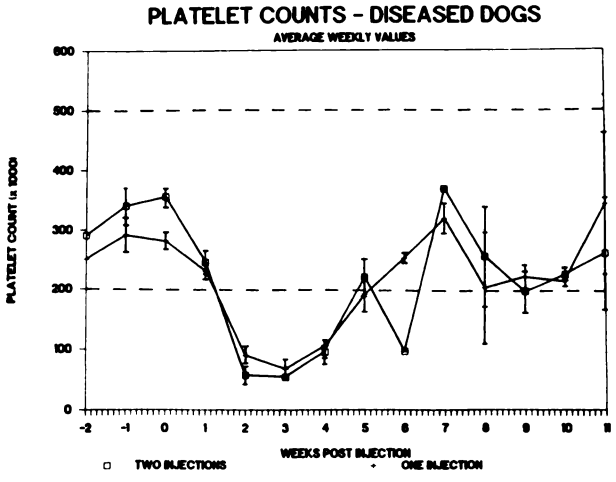

FIGURE 7
Platelet counts in dogs with assorted skeletal neoplasms before and for 10 wk after treatment with ^{153}Sm-EDTMP. Graphs are for two treatment groups, 1 mCi (37 MBq)/kg once and 1 mCi (37 MBq)/kg twice with 1 wk between the two injections. The graphs indicate the recovery delay imposed by the second injection and the return to normal levels (200,000–5000 cells/microliter) at roughly 4 wk after the last radiopharmaceutical injection. No animal exhibited any clinical evidence of increased bleeding tendency during the time that counts were reduced.

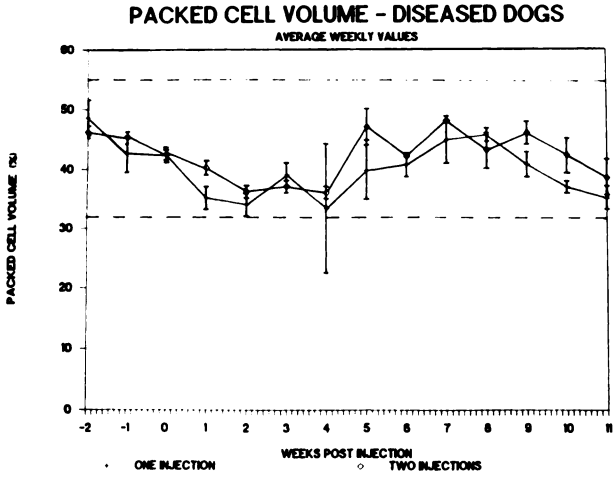

FIGURE 8
Packed cell volumes of dogs with various skeletal neoplasms before and for 10 wk after treatment with ^{153}Sm-EDTMP. Graphs are for two treatment groups, 1 mCi (37 MBq)/kg once and 1 mCi (37 MBq)/kg twice with 1 wk between the two injections. The graphs indicate a mild decrease in the PCV for both groups during the first 5 wk after injection of the radiopharmaceutical. The lowest average level reached is still considered to be within the normal range for dogs (32%–55%). No dog was ever considered clinically anemic.

revealed no significant response differences ($p > 0.05$) for the BUN, ALP, ALT, platelets, and WBC counts. There was, however, a significant response difference for the PCV values at Weeks 2 and 3 ($p = 0.05$ and $p = 0.04$, respectively) detected.

When the cell count values of the treated diseased dogs, taken as a group, were compared to untreated normal control beagles housed under similar conditions a significant difference ($p < 0.05$) in the change scores was detected. The points at which significant count reductions existed were Weeks 3 and 5 for the PCVs, Weeks 3 and 4 for the WBC counts, and Weeks 3, 4, and 5 for the platelet counts.

As in the experiments in normal beagles, the serum electrolytes did not respond to the administration of the ^{153}Sm-EDTMP in any discernible way. The responses of the serum enzymes ALP and ALT as well as the BUN levels (measured at weeks 0, 1, and 4) were also similar to those seen in the normal dog studies. No significant differences ($p > 0.05$) were detected between the two dose groups for these parameters.

The patient dogs have not demonstrated evidence of toxic side-effects in organs considered at risk (liver, kidneys and bone marrow) attributable to the treatment other than the bone marrow effects. Although changes in hematologic and biochemical parameters have been detected on follow-up in some cases, these have generally been associated with a demonstrable cause (e.g., renal failure, pulmonary metastasis), which was considered to be unrelated to the radioisotope treatments.

Postmortem examinations in 33 of the diseased patient dogs, at post-treatment intervals of up to more than one year, have failed to reveal any evidence of lesions attributable to radiation injury or toxic effects of the chelate itself. Numerous sporadic lesions were observed, however the number and types of lesions seen were not considered unusual for the age and debilitated nature of the animals. Furthermore, no discernible pattern of lesion occurrence in the treated dogs which cannot be attributed to the animals' primary disease has emerged.

DISCUSSION

Our data indicate that the lesions most likely to respond to treatment are those which have not yet broken through the cortex of the bone, small metastatic lesions (lesions < 2.0 cm in diameter), and those tumors involving the axial skeleton.

When the radiographs indicated that the neoplasm either arose from the periosteum or had broken through the cortex, the uptake of the ^{153}Sm-EDTMP and ^{99m}Tc-MDP was generally nonuniform. Patients with lesions of this type responded less dramatically to treatment and if palliation did occur it was generally of shorter duration than that in lesions which had uniformly intense uptake of the radioisotopes.

Large, noncalcified, periosteal tumor components did not take up the radioisotopes and did not respond to the treatment. Most of the far-advanced primary tumors fell into this group.

Since the ^{153}Sm-EDTMP chelate had lesion discrimination essentially identical to that of ^{99m}Tc-MDP, (Fig. 5) (*16,17,19*) the technetium bone scan is a reasonable predictor of the selectivity and the effectiveness of this chelate for a given lesion.

It is interesting that the two treatment groups failed to exhibit significant differences in response between them. The degree of bone marrow depletion and lesion control was virtually identical for the two groups. This would seem to indicate that the initial treatment was effective in delivering a therapeutic dose to all of the tumor cells which could be reached by this treatment modality. The remainder of the tumor cells, those responsible for treatment failure, were apparently sequestered from the radiopharmaceutical. The short period of time between the two injections was apparently insufficient to permit tumor cells to be redistributed to an accessible position or, alternately, these cells were not capable of localizing the samarium. The observation that large, nonossified lesions were the poorest responders may indicate that deposition of the chelate is tied to matrix formation and therefore foci of non-matrix-forming cells greater in size than the 3-

mm maximum range of ^{153}Sm beta particles would be protected from deposition of significant doses of radiation within them. The good response of heavily calcified lesions even when quite large (Fig. 2) would also support this line of reasoning.

The observed resiliency of the bone marrow could also be explained by this mechanism. Bone marrow cells located within the shafts and large trabecular spaces of the long bones would be protected by their physical location. Inactive or dormant cells in such locations may also be less susceptible to low doses of radiation then the actively proliferating stem cells of the active marrow. Further work needs to be performed to evaluate this aspect.

The good response of metastatic lesions may be due to the relief of pain caused by irradiation of the invasion interface of the tumor locus with the normal bone. The osteoblastic activity would generally be increased at this zone and therefore good localization would be expected. If the diameter of the lesion was less than the average range of the beta particle then therapeutic irradiation of the entire nodule would occur. Whether or not total irradiation of the nodule occurred, destruction of the neoplastic cells at the interface with the normal bone would alleviate the patient's pain.

Dogs, like humans, have spontaneously occurring neoplastic disease arising from a variety of tissues. In many instances canine tumor kinetics are quite similar to those of human tumors (*20–26*). Brodey provides a review of the numerous studies in which canine tumors have been used as models of the same tumor in humans (*22*). The response of both the dog and the neoplasm to treatment closely parallels that encountered in the human.

Primary skeletal neoplasia is relatively common in dogs, with an estimated incidence of 7.9 cases per 100,000 animals or ~8,000 new cases occurring annually in the U.S. (*27,28*). The natural history, signalment, progression and site of occurrence parallels that of human osteosarcoma. The use of canine primary osseous tumors as a model for both primary and metastatic skeletal neoplasia in human is justified since the primary tumor is, if anything, less likely to respond to systemic therapy than a metastatic one (*20, 29*). Therefore, any agent which shows an effect on primary tumors could be expected to similarly affect metastatic ones. Tumor kinetics and growth within the bone are probably similar except for the production of matrix in primary tumors. Even this is not universal within a given primary tumor, as markedly inhomogeneous cell populations, some of which do not form a matrix, are common (*21–23,29*).

The reasons for the rapid recovery of the bone marrow origin cell populations are not well understood. A number of explanations are possible but the most probable one is that the bone marrow does not receive radiation doses which are nearly as high as those delivered to the bone matrix. Dose calculations based on NCRP data and formulas and experimental results of biodistribution studies in rats and rabbits (*17,19,30*) estimate the red bone marrow dose in an adult human to be ~0.74–1.03 mGy/MBq (2.75–3.82 rad/mCi) for each mCi of injected dose. Using a standard mass of 70 kg for an adult human, then estimate the red marrow dose from a 37-MBq (1 mCi/kg) intravenous dose of ^{153}Sm-EDTMP at 51.8–72.1 mGy (192.5–267.4 rads). While a direct correlation between humans and dogs may not be explicitly accurate, it is unlikely that the differences are significant enough to alter the assumption that the marrow dose in dogs is similar to that calculated for humans. While these doses are likely to cause some myelosuppression, sterilization is unlikely.

Alternately, dormant but recruitable bone marrow cells such as those residing in the marrow cavity of long bones may be less susceptible to radiation effects because of their dormant nature or geographical location. Subjective evidence of increased bone marrow activity in biopsies taken from the proximal femur of normal beagles administered ^{153}Sm-EDTMP tends to support this hypothesis (*18*). Recently, published data from normal dogs given larger doses (up to 1.29 GBq (35 mCi/kg) of ^{153}Sm-EDTMP indicating that these dogs were able to recover from the bone marrow depletion resulting from doses at this level also indicates the apparent resiliency of the bone marrow where this agent is concerned (*31*). In any case, the rapid recovery of the marrow in these diseased dogs demonstrates that the presence of the disease state does not appreciably alter the ability of the bone marrow to respond to the depletion of stem cells incurred by this treatment.

A recent report (*32*) deals with both the response and the adverse side effects encountered when human patients with skeletal metastasis from tumors of soft-tissue origin were administered doses of ^{153}Sm-EDTMP in the 3.7–37 MBq/kg range. These patients did experience some pain relief and did not undergo unacceptable depression of the circulating white cell and platelet counts or any other adverse side effect. The degree of palliation achieved was variable but was prolonged in some patients. The findings of both this study and our own justify continued development of this radiopharmaceutical for use in treatment of metastatic skeletal neoplasia.

SUMMARY

Biochemically targeted beta-particle radiotherapy has been shown by this study to have significant antitumor activity. Palliative and even curative effects have been demonstrated in dogs using ^{153}Sm-EDTMP to treat a variety of skeletal neoplasias, both primary

and metastatic. The primary side effect was a transient subclinical bone marrow depression which affected all cell lines, resulting in marked reductions in circulating peripheral blood counts for platelets and white cells and mild reductions in the PCV. The cell counts recovered to normal levels within one month of the last injection of radiopharmaceutical. A mild immediate increase in serum alkaline phosphatase levels was seen in most animals but no other evidence of liver injury was observed. None of the animals in the study had clinically evident adverse reactions or side effects from the administration of the radiopharmaceutical. Postmortems of dogs dying while on the study failed to reveal any lesions attributable to the radiopharmaceutical. The findings in this study indicate that further exploration of ^{153}Sm chelates as therapeutic radiopharmaceuticals is warranted.

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Radioiodine-125

William G. Meyers, PhD, MD and Johannes Cornelis Vanderleeden, MSc

Iodine-125 with a half-life of sixty days is next to the longest lived among the 21 radioactive isotopes of iodine. Its specific acivity of 644 million disintegrations per second per microgram makes it suitable as a tracer in investigations of the metabolism of stable iodine-127.

Studies in this laboratory indicate that chiefly because of the absence of beta particles radiation exposures will always be much less when iodine-125 is used in place of iodine-131 in diagnostic tracer applications.

The low energies of the quanta make iodine-125 especially suitable for labeling compounds and substances such as iodinated serum albumin, iodinated fat, and diiodosulfanilate for in vitro assays, as well as piodophenye sulfonyl chloride (pipsyl chloride) and similar compounds for iosotope derivative analyses because of the high efficiency with which the photons are measurable.

Autoradiographs made in cytochemical and histochemical studies by means of iodine-125 should provide exceptionally high resolution because of the short ranges in cells and tissues of the Auger and internal conversion electrons.

Some of the principal advantages for radioiodine-125 for applications to the life sciences are summarized as follows:

1. Soft 27.4-35.4 keV X-rays and Y-rays for improved "photon projection analysis."

2. No beta particles; lower radiation exposures; soft photons; protection is simplified.

3. 60-day half-life; convenient "shelf" time; economy; infrequent synthesis and shipping.

4. High resolution autoradiography with soft Auger and internal conversion electrons. ■