Editorial: "Systemic Radioisotopic Therapy of Primary and Metastatic Bone Cancer"

Interest in radioisotopic therapy is on the rise, and justifiably so. The promise of targeting treatment with monoclonal antibodies and receptor-specific compounds has created considerable excitement regarding its future role in medicine. From a practical point of view, however, the use of precursor targeted radiopharmaceuticals in the treatment of primary and metastatic cancer to bone is likely to provide more immediate results for applications in nuclear medicine practice over the next decade.

As detailed elsewhere in this issue of the *Journal* (Lattimer, et al.), the potential for significant palliation of primary bone tumors, and in some cases potential cure, has been raised. Taking advantage of the spontaneous occurrence of skeletal neoplasia in dogs, Lattimer and co-workers devised a careful, prospective evaluation of samarium-153-EDTMP (ethylenediaminetetramethylenephosphonic acid.) In all, 40 animals with osseous or nonosseous sarcomas of the skeleton were treated. Two animals had complete involution of chondrosarcomas. Seven dogs were found to be alive over 11 mo after treatment with a mean survival time of 27 mo. Four of those seven responders later had amputation or other treatment; two of those four are still alive after three years. Twenty-five of 40 dogs showed a partial response to treatment and later developed recurrence. Eight dogs with far advanced disease failed to show significant clinical improvement.

In this study of spontaneous sarcomas, lesions most likely to respond were those that had not yet broken through the bony cortex, metastatic deposits <2.0 cm in diameter, and lesions that originated in the axial skeleton. Dogs with wide-spread tumor bulk were least likely to respond. Uptake by technetium-99m-MDP on bone scan predicted ^{153}Sm-EDTMP uptake and response. This suggests that the standard ^{99m}Tc-MDP bone scan may predict those likely to respond to therapy. The authors state that the beta radiation of ^{153}Sm ($E_{\beta\ max}$ = 0.80 MeV, $T_{½}$ = 46.8 hr) has a maximum range in tissue of ~ 3 mm. They postulate that the mechanism of action is destruction of neoplastic cells at the interface of tumor with normal bone. The work of Lattimer et al. is important, not only for the clinical benefit provided to the dogs studied, but because of the implications for treatment of all patients with primary and metastatic tumor to bone.

The use of targeted radioactive precursors as primary therapy for tumors originating in bone has considerable appeal. The avid concentration of various labeled phosphates and ionic strontium-89 (^{89}Sr) in osteogenic sarcoma (*1*) suggests that the use of one or more of these compounds with curative intent is not out of the question. Although significant strides in the therapy of primary and recurrent osteogenic sarcoma have been made over the past two decades, management of these tumors is still difficult (*2*). The use of bone-seeking radioisotopes as adjunct and potentially curative therapy in osteogenic sarcoma should be investigated.

A much larger group of patients who should be treated by beta-emitting bone-seeking radiopharmaceuticals include those with metastatic carcinoma of prostate and breast. Prostate cancer is now the most common tumor in men and the second most common cause of death in males in the United States. Carcinoma of the breast is the most common cancer affecting females over the age of 40. Nearly 50% of patients with breast or prostate cancer will eventually develop bone metastases. Previous work by the University of Missouri group has shown preferential localization of ^{153}Sm-EDTMP in metastatic bone lesions in humans (*3*).

In addition to ^{153}Sm-EDTMP, other bone-seeking therapeutic radiopharmaceuticals are under investigation. Strontium-89-chloride and rhenium-186 (^{186}Re) (Sn)HEDP) have been reported to provide excellent palliation of painful skeletal metastases (*4–9*). All three of these agents provide high tumor-to-normal bone ratios in prostate and breast cancer, with acceptable hematologic toxicity. All three compounds may be used for repeated treatments. At our own institution, we have now treated almost 400 patients for metastatic cancer to bone with ^{89}Sr, including over 250 patients with metastatic prostate or breast cancer. To date, 79% of our patients with metastatic prostate cancer have responded to ^{89}Sr therapy with decreased bone pain and improved quality of life. Our response rate in breast cancer is 83%. Similar clinical results with ^{89}Sr have been found in a prospective treatment protocol and in a double-blind treatment protocol with ^{89}Sr sponsored by Amersham Corporation in England (Bayly RJ, *personal communication*, 1990). Maxon has reported an 80% (16 of 20) response rate in patients with hormonally resistant prostate cancer treated with ^{186}Re (Sn)HEDP (*8*). There are some patients, perhaps 10%–20% of those with metastatic prostate or breast cancer,

Received May 30, 1990; revision accepted May 30, 1990.
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who do not respond to internal radioisotopic or external beam radiation therapy.

The current primary indication for systemic radioisotopic therapy of metastatic cancer is bone pain. Patients' symptoms should be carefully evaluated to determine whether or not their pain is in fact due to metastatic disease to bone, not from osteoarthritis, nerve root compression, or other musculoskeletal problems. Our new radioisotopic therapy is only going to be of use in those patients whose symptoms are the result of tumor involvement of bone. We can now say that there is no longer any reason for the vast majority of these patients to hurt. We will evolve to a point where we will be more aggressive in the treatment of patients with known metastatic disease who do not have significant bone pain.

The *treatment* of a cancer patient demands a different approach than the *diagnostic* mentality we are used to in nuclear medicine. The patient must be evaluated as a whole. Patients may have multiple organ systems involved by tumor and are likely to have concomitant diseases because of the age range of the patients. Each patient must be evaluated individually. Management of pain in the cancer patient is often poorly handled (*10*). Since the nuclear physician will often be seeing a patient who has little or no soft-tissue involvement, we believe an aggressive approach to the handling of their skeletal pain is in order. These are not easy patients to treat, but they are, as a group, among the most cooperative you will see because of their concern. They are also among the most grateful patients you will have, as they appreciate any relief from the continuous, toothache-type of pain they must endure.

Systemic radioisotopic therapy utilizes the basic tracer principles of nuclear medicine. The mechanisms of uptake of labeled phosphonates and elemental strontium are well known to nuclear physicians. Systemic radioisotopic therapy holds great promise for the near future. We should soon have available one or more bone-seeking therapeutic pharmaceuticals, including ^{89}Sr-chloride, and one or more of the labeled phosphonates. The nuclear physician needs to be aware of these developments, and incorporate bone-seeking radiopharmaceuticals into his or her practice as soon as they become available.

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