

## Radionuclide Therapy of Osseous Metastatic Disease

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*This is the first article in a series of four on nuclear medicine oncology procedures. Upon completion, the technologist will be able to describe the development of osseous metastases, state the treatment goal, and list the therapy's advantages and disadvantages.*

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Eckelman (1) recently discussed several promising radiopharmaceuticals for the treatment of osseous metastatic disease. This article examines the properties of three of these agents, which are currently under clinical investigation.

### HISTORY OF TREATMENT WITH RADIONUCLIDES

From its very inception, nuclear medicine has focused on both the diagnosis and treatment of disease. Early investigations with radiotracers yielded the ability to visualize and measure the metabolic activity of the thyroid with radioiodine. It was a short step from diagnosis to attempts at treatment with the same radionuclide that furnished the diagnosis.

Early attempts to image the skeleton used isotopes of strontium, calcium, and barium; strontium-85 ( $^{85}\text{Sr}$ ) nitrate eventually was made available by three commercial manufacturers in the United States. Due to the high radiation dose associated with  $^{85}\text{Sr}$ , use of this agent was limited to patients with known metastatic disease. Investigations soon centered around  $^{87\text{m}}\text{Sr}$ , with its shorter half-life and more desirable low-energy photons. After the advent of generator systems for easy production of technetium-99m ( $^{99\text{m}}\text{Tc}$ ), with its ideal imaging characteristics, bone-seeking agents labeled with this radionuclide soon became the standard for diagnostic imaging of the skeleton. The search for radionuclides able to treat bone disease discovered with  $^{99\text{m}}\text{Tc}$  bone-imaging

radiopharmaceuticals has led us back to some of the earlier bone-seeking agents.

### REVIEW OF BONE PHYSIOLOGY

There are two main types of bone: compact and cancellous. The compact or cortical bone is solid and composed of small cylindrical structures called haversian systems. These consist of a small central channel containing the nourishment supply surrounded by concentric lamellae of collagen, the organic matrix. Hydroxyapatite crystals, deposited along the collagen fibers, form the mineral matrix of the bone. Compact bone is the major component of the long bones, and also forms the outer shell of the predominantly cancellous bones such as vertebral bodies.

Cancellous (spongy) bone is composed of a network of interconnected plates surrounded by bone marrow. This type of bone is much less dense than cortical bone, although it provides a certain amount of support when present in normal amounts. Because of its larger surface area and its greater exposure to marrow (and the hematopoietic cells present in the marrow), cancellous bone is more metabolically active than cortical bone.

The skeleton provides structure, support, and protection for soft tissues and vital organs. The bony structure undergoes continuous remodeling and revision in its normal state. Bone remodeling is the process by which damaged cells are removed and new collagen and hydroxyapatite are deposited (2).

Metastatic disease to bone occurs via transport of malignant cells to the marrow (in cancellous bone) or to the nourishment center (in compact bone). The malignant cells cause disruption in normal bone remodeling and soon replace the normal cells, which results in loss of strength and eventual fracture. Eventually, metastatic replacement of normal bone will produce pain, causing loss of motion and severely affecting the patient's quality of life.

### OVERVIEW OF METASTATIC BONE DISEASE

Metastatic disease to bone is often the first presentation of distant disease in patients with diagnosed primary tumors.

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Osseous metastases are common in patients with cancers of the breast, lung, and prostate. Autopsy series have shown that up to 85% of patients who die with these cancers have metastatic disease to bone.

The goal of treatment in metastatic bone disease is to preserve function and improve the quality of life. During the progress of oncologic disease, pain becomes a major clinical management problem. Bone pain secondary to metastatic disease is a contributor to the intractable cancer pain syndrome. While the prognosis for patients with osseous metastases from cancers of the breast, lung, and prostate is variable, management of pain in patients suffering from these diseases can contribute to improvement in the quality of their lives.

The most common sites of bone metastases are: (1) vertebral body metastasis, producing neck and back pain with or without co-existing epidural spinal cord compression; (2) metastasis to the pelvis and femur, producing low back or lower extremity pain with associated mechanical instability and incident pain; and (3) base-of-skull metastasis, with associated headache and cranial nerve palsies (3).

Treatment of osseous metastatic disease is approached in several ways. At present, therapeutic options include chemotherapy, hormone manipulation in endocrine-dependent tumors, administration of agents that inhibit bone resorption, surgery, and radiation therapy. Two types of radiation therapy are currently in use: external body irradiation (either hemibody or selected site) and systemic administration of radiopharmaceuticals.

External body irradiation to selected sites is most effective in patients with one or a few discrete symptomatic sites. Hemibody irradiation, which can address multiple symptomatic sites, delivers an even distribution of the radiation dose to the affected half of the body with concomitant irradiation of nontumor sites. This approach can produce side effects that are not useful and may even be harmful to the patient.

The most common of these side effects is marrow suppression. Probably the most debilitating side effect to the patient is the nausea and vomiting that occur as the cells of the gastrointestinal tract are sloughed. This side effect is frequently not relieved by the usual medications. Systemic radionuclide therapy, with correct selection of the carrier and the radioisotope, can yield good results, with less nontarget irradiation.

### SELECTION OF RADIONUCLIDES FOR TREATMENT

Developing effective radionuclide therapy for osseous metastatic disease requires careful selection of the radionuclide with attention to several important features. A guiding principle in the choice of a radiopharmaceutical for therapy is to try to obtain a high target-to-nontarget ratio. Deposition of the radiopharmaceutical in the tumor at the highest possible concentration relative to nontumor tissues allows the highest deposition of energy (radiation) to the desired area.

Choices are available for this application in three general categories. Alpha-emitters, beta-emitters, and Auger electron-emitters following electron capture. All have important

features that can be useful in treatment of skeletal metastases (4).

Alpha particles and Auger electrons have very short ranges in tissue and deposit their energy in a very concentrated way (high linear energy transfer [LET]). Since the radiation travels only a short distance, the radionuclide must accumulate inside the tumor cells before decay in order for the treatment to be effective. The fact that alpha particles and Auger electrons deposit their energy in a concentrated manner is desirable because surrounding nontumor tissues receive less of the radiation. These physical properties of the emitted particles impose stringent requirements on the nature of the carrier compound, but, if the requirements are met, the compound could provide a high therapeutic yield.

The energy (LET) and range of beta-emitting radionuclides defines the list of nuclides suitable for development as therapeutic agents. The target (tumor or metastatic site) must receive a large fraction of the beta-emitter energy in order for treatment to be effective. If too large a fraction of the energy misses the target, an inhomogeneous treatment distribution can be expected. If the range of the beta particle is excessive in relation to the size of the target, increased radiation to surrounding tissue will result.

The half-life of any radionuclide being considered for treatment of metastatic disease is important. Ease of distribution from the production site, as well as the duration of any therapeutic effect and the scheduling of treatments (e.g., for fractionated or single-dose treatments), will be affected by the choice of radionuclide. The biological half-life of the carrier molecule, both in normal tissue and in tumor, is also a factor in development of a therapeutic agent. The physical half-life of the nuclide must be matched to the biological half-life of the carrier to maximize the energy deposition within the tumor, while minimizing the exposure to normal tissue.

The clinical utility of several beta-emitting radionuclides in the treatment of metastatic bone disease is currently being investigated. The physical properties of these radionuclides are summarized in Table 1. A discussion of their physical characteristics and preliminary clinical data follow.

TABLE 1. Beta-Emitting Radiol isotopes

Isotope	Half-Life (days)	$E_{\max \beta}$ (MeV)	$E_{\gamma}$ (keV)
Phosphorus-32	14.3	1.71	—
Samarium-153	1.9	0.81	103 (29%)
Strontium-89	50.5	1.43	—
Rhenium-186	3.7	1.07	137 (9%)

### Phosphorus-32

Phosphorus-32 ( $^{32}\text{P}$ ) has a physical half-life of 14.3 days and decays solely by beta emission. Its maximum beta energy is 1.71 MeV with a mean energy of 0.695 MeV. With this energy range, the average tissue penetration is 2–3 mm. Due to the abundance of phosphorus in bone,  $^{32}\text{P}$  has been

under investigation for use in the treatment of bone metastases for many years. Investigations in the 1940s showed evidence that radiophosphorus accumulated in sites of bony metastatic disease with some relief of pain and reduction of osteoblastic activity.

### **Samarium-153**

Samarium-153 ( $^{153}\text{Sm}$ ) is a beta-emitting radionuclide produced by neutron activation of a stable target. It has a half-life of 1.95 days (46.27 hr) and a maximum beta energy of 810 MeV. There is also a 29% abundant 103 keV gamma photon which is suitable for conventional scintigraphy. The average penetration range of the beta particle is 0.83 mm in water.

When complexed to ethylenediaminetetramethylene phosphonic acid (EDTMP), studies in animals show 50%–66% bone uptake within 2 to 3 hr. An additional 33%–50% of the complex is excreted in the urine within 8 hr of injection (5).

Early studies in five patients with metastatic bone cancer showed similar patterns of uptake of  $^{153}\text{Sm}$ -EDTMP and  $^{99\text{m}}\text{Tc}$ -hydroxydiphosphonate on scintigrams. Comparison of activity in the lesions with normal bone activity (target-to-nontarget) yielded similar ratios for both the radiopharmaceuticals, indicating a good potential for  $^{153}\text{Sm}$ -EDTMP in the treatment of osseous metastatic disease (5). Further clinical trials investigating the analgesic effects of  $^{153}\text{Sm}$ -EDTMP are underway.

### **Strontium-89**

Strontium-89 ( $^{89}\text{Sr}$ ) is a beta-emitting radionuclide produced by neutron activation of a stable target. It has a 50.5 day physical half-life and a principal beta emission of 1.43 MeV. It has no associated gamma radiation. Strontium-89

was the first radioisotope investigated for use in therapy of metastatic disease to bone. As early as 1942,  $^{89}\text{Sr}$  was shown to be effective for treatment of pain in patients with metastatic prostate cancer (6).

Early studies also revealed that concentrations of  $^{89}\text{Sr}$  in metastatic lesions remain higher than the concentration in adjacent normal bone. The concentration of strontium in normal bone decreases with time, while the concentration in abnormal sites remains relatively stable for up to 100 days (7). This preferential uptake in abnormal bone and maintenance of the relatively high concentration indicate the potential for excellent treatment results. Robinson et al. (8) have shown promising results after use in nearly 500 patients.

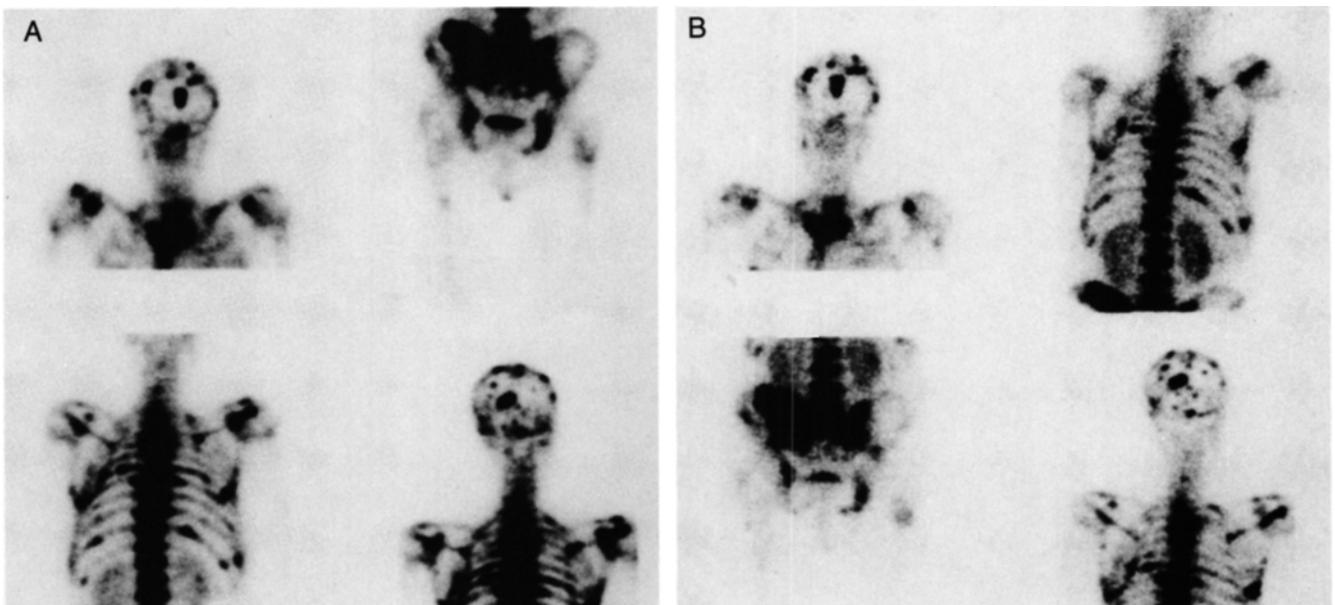
### **Rhenium-186**

Rhenium-186 ( $^{186}\text{Re}$ ) is a beta-emitting radionuclide with a maximum beta emission of 1.07 MeV. It has a 9% abundant gamma ray of 137 keV which is suitable for imaging. The half-life of 3.7 days makes this a potential candidate for use in treatment of metastatic bone lesions. Rhenium-186 has been complexed to hydroxyethylidene diphosphonate (HEDP) for use in treatment of osseous metastatic disease (see Fig. 1).

A series of 51 patients treated with  $^{186}\text{Re}$ -HEDP showed improvement in quality of life variables measured during this clinical trial (9).

## **HANDLING OF BETA-EMITTERS IN THE RADIOPHARMACY**

It is of utmost importance that the technologist be aware of the type of energy being emitted by therapeutic agents. Beta



**FIG. 1.** Diagnostic and therapeutic bone scans in a male patient with metastatic prostate cancer illustrating identical uptake patterns. Radiopharmaceuticals used were (A)  $^{99\text{m}}\text{Tc}$ -HDP and (B)  $^{186}\text{Re}$ -HEDP. (Images courtesy of B.A. Zonnenberg, MD, PhD, University Hospital Utrecht, Utrecht, The Netherlands.)

particles are generally not regarded as an external radiation hazard. The particles penetrate skin to a depth of a few millimeters; therefore, direct exposure should be avoided. The shielding of a plastic syringe is often sufficient to completely attenuate any beta radiation from its contents. For higher energy beta emitters, the addition of a plastic sleeve should be considered.

If the nuclide also emits gamma radiation, the amount of that exposure can be estimated by multiplying the abundance of the gamma by the dose to be administered. For instance, while a 30 mCi dose of  $^{186}\text{Re}$ -HEDP emits gamma radiation equivalent to  $\sim 3$  mCi of  $^{99\text{m}}\text{Tc}$ , an equal dose of  $^{153}\text{Sm}$ -EDTMP emits gamma radiation equivalent to 9 mCi of  $^{99\text{m}}\text{Tc}$ . A 30 mCi dose of  $^{32}\text{P}$  would not emit external radiation.

### CONCLUSION

All of the radionuclides discussed above have undergone or are in the process of evaluation for efficacy in the treatment of pain associated with osseous metastatic disease. The primary purpose of such treatment is the relief of pain and improvement in the quality of life for patients suffering from various types of cancer. Since measurement of pain relief is subjective at best, the results of treatments of this type are

difficult to measure. Double-blind placebo-controlled trials must be completed before the final verdict is rendered on any of these potential agents.

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