INVITED COMMENTARY

Advances in Our Understanding of the Treatment of Painful Bone Metastases

Rhenium and technetium are both members of group 7A of the periodic table. ^{186}Re and ^{188}Re are β-emitting radionuclides and, therefore, theoretically can be substituted for ^{99m}Tc by reactions analogous to those used to produce technetium-labeled radiotracers such as ^{99m}Tc-etidronate, an early bone scintigraphic agent. The use of ^{186}Re-etidronate (hydroxyethylidene diphosphonate) as a potential β-emitting radiopharmaceutical for the treatment of pain from bone metastases was first suggested in 1979 (not 1987) by Mathieu et al. (*1*), who performed the initial chemical preparation and animal biodistribution studies. Rhenium complexes are thermodynamically stable in their higher oxidized state, so reduced rhenium complexes tend to reoxidize back to perrhenate. Deutsch et al. (2) solved this radiopharmaceutical problem by stabilizing and purifying rhenium etidronate. Mallinckrodt Inc. subsequently purchased the rights to this material. Unfortunately, delays in ^{186}Re-etidronate development have led to a suspension of its production in the United States, although it is widely used in Europe.

Rhenium etidronate injected intravenously quickly diffuses into the extravascular space. The phosphonate moiety may have a role in chemisorption of rhenium to hydroxyapatite, but evidence also exists of metal transchelation to an oxygen of hydroxyapatite with hydrolysis. The hydroxyapatite–rhenium bond is not as stable as that of samarium, and reoxidized perrhenate may be found in the urine for up to 72 h, whereas urinary excretion of samarium is complete in 6 h.

^{186}Re (half-life, 90 h, with a 137-keV γ, 1.07- and 0.93-MeV βs), a reactor product, contains carrier ^{185}Re and ^{187}Re and usually is contaminated with a small amount (1%) of ^{188}Re. ^{186}Re has in the past been more easily produced than the carrier-free ^{188}Re (155-keV γ, 2.12-MeV β), although the latter is now available from a ^{188}W generator (*2*). Thus, virtually all published clinical data using rhenium for the reduction of bone pain from osteoblastic (seen on bone scans) metastatic disease are from the use of ^{186}Re-etidronate.

^{186}Re-etidronate is one of several radiopharmaceuticals that have been used to reduce or eliminate the pain of osteoblastic bone metastases. These radiopharmaceuticals have β, electron, or low-energy x-ray emissions that travel short distances from the bone surfaces to which radionuclide chemisorption or incorporation has occurred before depositing their energy in the adjacent tumor that has stimulated osteoblastic activity. The radiopharmaceuticals currently in use to treat painful bone metastases are listed in Table 1 (*2*). Although ^{89}Sr and ^{32}P do not emit γ rays, their bremsstrahlung may be used for imaging and dosimetry just as the γ rays may be (*3,4*).

Most of the published clinical studies using ^{186}Re-etidronate are summarized in Table 2 (*4–13*). The activity used is generally approximately 1295 MBq, although it is of interest that escalating the activity from 1295 to 1850 to 2405 MBq in a study from Utrecht increased the response rate from 33% to 78%. Further increments did not improve the response rate but were myelotoxic (*6*). With 1295 MBq of injected ^{186}Re-etidronate, investigators have found response rates of 60%–80% (*4–13*). The range of response rates may be caused by differences in the populations treated, in the schema of measuring response, or, less likely, in the activities administered. In fact, all the radiotracers listed in Table 1 have yielded a similar range of response rates, regardless of the way they have been measured.

One of the most appealing approaches to measuring the response to a radiopharmaceutical given to ameliorate the bone pain of osseous metastases is the "3-dimensional" Utrecht schema that integrates pain reduction, activities of daily living, and medication index (*6*). Thus, a reduction in pain would not be graded as a response to treatment if the patient was spending more time in bed.

The careful experimental design of the study by Sciuto et al. (*14*) reported in this issue of *The Journal of Nuclear Medicine* is a model of the use of the best investigative materials and methods currently available to tackle the difficult problem of measuring changes in bone pain in cancer patients, including the Utrecht scale. Inclusion criteria are clear and presumably involved negative pregnancy test results in women of childbearing age. Exclusion criteria can be largely inferred, but one cannot tell whether the investigators screened for disseminated intravascular coagulation. The "increased ^{99m}Tc-MDP uptake in multiple skeletal foci" presumably included increased uptake in the most painful focus, whereas cord or nerve compression and impending pathologic fracture must be exclusion criteria. *P* values "slightly greater than" 0.05 were considered of marginal significance and may or may not be important. Readers must make their own judgment.

The hospital isolation of the patients

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TABLE 1
β- or Electron-Emitting Radiopharmaceuticals for Painful Metastases

Radiopharmaceutical	Half-life (d)	Maximum E_β (MeV)	Mean E_β (MeV)	Maximum tissue range (mm)	Mean tissue range (mm)	γ Half-life (MeV)
^{188}Re(Sn)-HEDP	0.7	2.12	0.73	11.0	2.7	0.155 (10)
			0.79		3.1	
^{153}Sm-EDTMP	1.9	0.81	0.23	2.5	0.6	0.103 (28)
						0.070 (5)
^{90}Y-citrate	2.7	2.27	0.94	11.1	2.5	—
^{186}Re(Sn)-HEDP	3.8	1.07	0.33	4.5	1.1	0.137 (9)
^{117m}Sn-DTPA	13.6	0.127*	NA	0.27	0.2	0.159 (86)
		0.152*	NA		0.3	
^{32}P-phosphate	14.3	1.71	0.70	7.9	3.0	—
^{89}Sr-chloride	50.5	1.46	0.58	7.0	2.4	0.909 (0.10)
^{85}Sr-chloride	64	0.025*	NA	—	10	0.514
						plus 10- to 15-keV
		0.040*	NA			x-rays

*Conversion electrons.
E_β = β energy; HEDP = hydroxyethylidene diphosphonate; EDTMP = ethylene diamine tetramethylene phosphonate; DTPA = diethylenetriaminepentaacetic acid; NA = not available.
Numbers in parentheses are percentage abundance.

in this study deserves comment, because in the United States, the Nuclear Regulatory Commission allows release of the patient to home if the closest household contact will receive no more than 5 mSv, with appropriate written instructions on radiation safety required when individuals at home may receive more than 1 mSv. This dosage equals 5.7 GBq (150 mCi) ^{186}Re, or 5.8 GBq (160 mCi) ^{188}Re (*15*), whereas the therapeutic dosage of ^{186}Re-etidronate is usually in the range of 1.3 GBq (Table 2).

This study showed response rates that did not differ to a statistically significant degree from those summarized in Table 2. The rates and degree of hematologic toxicity and flare were also similar to those in the studies of Table 2. Sciuto et al. (*14*) reconfirmed a

TABLE 2
^{186}Re-Etidronate Efficacy

Study	Cancer type	No. of patients	Dose	Response (%)
Han et al. (*7*)	Breast	24	1295–2960 MBq (35–80 mCi)	58
Hauswirth et al. (*8*)	Breast	17	1295 MBq (35 mCi)	59
Limouris et al. (*9*)	Prostate	16	1400 ± 100 MBq (37.8 ± 2.7 mCi)	81
Limouris et al. (*10*)	Breast	14	1400 ± 100 MBq (37.8 ± 2.7 mCi)	71
Schoeneich et al. (*11*)	Prostate or breast	44	1295 MBq (35 mCi)	60
Holle et al. (*12*)	Prostate	15	1810–2590 MBq (49–70 mCi)	87
Quirijnen et al. (*6*)	Prostate	18	1295 MBq (35 mCi)	33
		9	1850–2405 MBq (50–65 mCi)	78
		10	2960–3515 MBq (80–95 mCi)	70
Maxon et al. (*13*)	Prostate, breast, miscellaneous	43	1258 MBq (34 mCi)	77
Schoeneich et al. (*11*)	Prostate, breast, miscellaneous	10 (second treatment)	1258 MBq (34 mCi)	50
Sciuto et al. (*14*)	Prostate, breast, miscellaneous	60	1406 MBq (38 mCi)	80

lack of difference in response rates between tumor tissue types. In agreement with previously published data (*16*), Sciuto et al. found no pretreatment variables that correlated with the degree of pain response to therapy.

The new findings in this paper, based on unique long-term follow-up data, relate to the positive correlation between duration of pain relief and degree of response and the negative correlation between duration of pain relief and both pretreatment scintigraphic score and serum alkaline phosphatase level. Perhaps a greater degree of pain relief was caused by a more extensive cytocidal effect of ^{186}Re-etidronate on a smaller tumor mass, and hence a longer time might pass before the tumor regrew enough to cause recurrent pain. By the same reasoning, with a higher tumor burden as reflected by the alkaline phosphatase level and the extent of abnormalities seen on bone scans, the number of cells killed would be less for the same administered activity, and pain relief would not be expected to last as long.

The response to a second treatment in this study echoed the Cincinnati ^{186}Re-etidronate data (*13*) and was lower than after the first treatment, probably because of a higher tumor burden by the time of the second treatment.

The correlations between degree of response and score on the Wisconsin pain test or Karnofsky performance scale were weak in this study ($r <$ 0.40), actually causing switched signs (positive to negative for pain and vice versa for performance) between short- and long-term responses. Also, the *P* values exceeded 0.05 for these correlation coefficients.

^{186}Re-etidronate compared very favorably with the other radiopharmaceuticals in Table 1 of Sciuto et al. (*14*), who claimed less clinically significant hematologic toxicity with ^{186}Re-etidronate than with ^{32}P and ^{153}Sm-lexidronam. The available data do not support this claim. Neither ^{32}P nor ^{89}Sr showed clinical myelotoxicity in a recent comparison in which ^{32}P-treated patients never had greater than grade 2 myelotoxicity. ^{89}Sr produced no grade 2 toxicity (*17*). In fact, to my knowledge the literature attributes only 1 death from thrombocytopenia to ^{32}P (*18*). ^{153}Sm-lexidronam has not been shown to cause any more, or less, hematologic toxicity at the usually accepted dosage, 37 MBq/kg, than does ^{186}Re-etidronate (*19*).

Contrary to the claim of Sciuto et al. (*14*) that absence of γ emission limits the usefulness of ^{32}P and ^{89}Sr for imaging and dosimetry, bremsstrahlung from these radionuclides has, in fact, been successfully used for these purposes (*3,4*). In fact, to my knowledge none of the radiopharmaceuticals in Table 1 has been shown to be more efficacious or significantly less toxic than any other in any published comparative trial. The myelotoxicity of ^{117m}Sn-pentetate could theoretically be less than that of the others because of the very short path of its emitted conversion electrons (*20*). A comparative study of ^{89}Sr and ^{117m}Sn-pentetate is in progress.

Therapy of painful bone metastases with unsealed sources began in the early 1940s, but we still do not know which tracer is best, whether asymptomatic patients with bone metastases should be treated, or even what the mechanism of the response is. Many questions remain for the nuclear medicine community to answer in this area of research as we strive to treat our patients' pain with radiopharmaceuticals.

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