Considerations in the Selection of Radiopharmaceuticals for Palliation of Bone Pain from Metastatic Osseous Lesions

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Bone pain is a common complication for terminal patients with bone metastases from prostate, lung, breast, and other malignancies. A multidisciplinary approach in treating bone pain is generally required, 1 which includes a combination of analgesic drug therapy, radiation therapy, hormonal therapy, and chemotherapy. Over the years, treatment of bone pain using bone-seeking radiopharmaceuticals has been explored extensively. Pharmaceuticals labeled with energetic β-particle emitters such as ^{32}P, ^{89}Sr, ^{153}Sm, and ^{186}Re, in addition to the low-energy electron emitter ^{117m}Sn, have been studied for this purpose. Bone-marrow toxicity as a consequence of chronic irradiation by the energetic β particles is a general problem associated with this form of treatment. It is therefore desirable to identify radiochemicals that minimize the dose to the bone marrow and at the same time deliver therapeutic doses to the bone. **Methods:** New S values (mean absorbed dose per unit cumulated activity) for target regions of human bone and marrow were used to ascertain the capacity of various radiochemicals to deliver a high bone dose while minimizing the marrow dose. The relative dosimetric advantage of a given radiopharmaceutical compared with a reference radiochemical was quantitated as a dosimetric relative advantage factor (RAF). Several radionuclides that emit energetic β particles (^{32}P, ^{89}Sr, ^{153}Sm, ^{186}Re, and ^{177}Lu) and radionuclides that emit low-energy electrons or β particles (^{169}Er, ^{117m}Sn, and ^{33}P) were evaluated. For these calculations, ratios of the cumulated activity in the bone relative to cumulated activity in the marrow α equal to 10 and 100 were used. **Results:** When the radiopharmaceutical was assumed to be uniformly distributed in the endosteum and α was taken as 100 for both the reference and test radiochemicals, the RAF values compared with the reference radionuclide ^{32}P were 1.0, 1.2, 1.4, 1.6, 1.7, 1.9, and 2.0 for ^{89}Sr, ^{186}Re, ^{153}Sm, ^{177}Lu, ^{169}Er, ^{117m}Sn, and ^{33}P, respectively. In contrast, when the radiopharmaceutical is assumed to be uniformly distributed in the bone volume, the RAF values for these 7 radionuclides were 1.1, 1.5, 2.4, 3.2, 4.5, 5.1, and 6.5, respectively. **Conclusion:** These results suggest that low-energy electron emitters such as ^{117m}Sn and ^{33}P are more likely to deliver a therapeutic dose to the bone while sparing the bone marrow than are energetic β emitters such as ^{32}P and ^{89}Sr. Therefore, radiochemicals tagged with low-energy electron or β emitters are the radiopharmaceuticals of choice for treatment of painful metastatic disease in bone.

Key Words: bone pain; radionuclide therapy; dosimetry

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The use of bone-seeking radiopharmaceuticals to relieve pain caused by osseous metastatic lesions has been a topic of considerable interest for more than 50 y. ^{32}P-orthophosphate (*1*) and ^{89}Sr-chloride (*2*) were the first radiochemicals to be evaluated for this purpose, with the first clinical use dating back to 1941. These radionuclides are energetic β emitters with mean energies (physical half-lives) of 695 keV (14.26 d) and 583 keV (50.53 d), respectively (Table 1). The relatively long range of these energetic β particles in soft tissue and bone (Table 1) can result in significant irradiation of the marrow compartment, which can lead to depression of bone marrow function. As a consequence, a great deal of research has been devoted to finding new radiochemical forms of ^{32}P and new radionuclides with more favorable radiation properties. Among the ^{32}P radiochemicals that have been studied are phosphonates and diphosphonate (disodium etidronate); however, these also resulted in high marrow toxicity (*3*).

The drawbacks associated with ^{32}P and ^{89}Sr as palliative agents have led to the search for other suitable radiochemicals. Among them are ^{186}Re-hydroxyethylene diphosphonate (HEDP) and ^{153}Sm-ethylene diamine tetramethylene phosphonate (EDTMP) (*4,5*). These radionuclides have physical half-lives of only 3.8 and 1.9 d and mean β particle energies of about 323 and 225 keV, respectively. The significant pain reduction observed for ^{153}Sm-EDTMP recently led to approval by the U.S. Food and Drug Administration (FDA) for its use in palliation of bone pain

Although the clinical efficacy of ^{153}Sm-EDTMP appears to be good (*6*), there is ample room for continued improvement in reducing bone pain and at the same time minimizing adverse effects to the marrow. Recent studies with the low-energy electron-emitter ^{117m}Sn were performed with this

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TABLE 1
Radionuclide Properties for Bone Pain Palliation Therapy

Radionuclide	Half-life (d)*	Mean β energy (keV)	Mean range in bone† (mm)	Yield/decay
^{32}P	14.26	695	1.7	1.0
^{33}P	25.34	76.6	0.05	1.0
^{89}Sr	50.53	583	1.4	1.0
^{117m}Sn	13.61	135‡	0.15	1.14
^{153}Sm	1.95	225	0.32	1.0
^{169}Er	9.40	100	0.09	1.0
^{177}Lu	6.71	133	0.15	1.0
^{186}Re	3.78	323	0.64	0.94

*Physical half-lives and mean energies taken from (*29*) and (*30*).
†Approximate range taken from International Commission on Radiological Units & Measurements Report 37 (*31*).
‡Conversion electron.

goal in mind (*7–9*). In this study, a theoretical framework is developed to aid in the selection of radiopharmaceuticals with optimal radiation characteristics that are likely to maximize the dose delivered to the bone and minimize the absorbed dose delivered to the red bone marrow. These calculations allow a physical comparison of the relative efficacy of various radiochemicals to meet the overall objective of this modality.

MATERIALS AND METHODS

Dosimetric Relative Advantage Factors

All radiopharmaceuticals that have been evaluated for bone pain relief are bone seekers; hence, the bone marrow is the critical organ for this modality. The principal goal for alleviating bone pain with radiopharmaceuticals is to deliver a sufficiently high radiation dose to the bone or bone tumor while delivering the lowest possible dose to the red marrow. The radiation properties of the radionuclide play a major role in achieving this goal. Consequently, it is of interest to compare the capacity of various radionuclides that, based on their radiation properties, are likely to meet the stated goal. One can quantify the advantage of a given radionuclide compared with a reference radionuclide using a quantity called the dosimetric relative advantage factor (RAF).

According to the MIRD formalism (*10*), the mean absorbed dose to a given target region r_T from radioactivity localized in source regions r_S is given by:

$$\bar{D}(r_T) = \sum_{\text{all sources}} \tilde{A}(r_S)\, S(r_T \leftarrow r_S), \qquad \text{Eq. 1}$$

where $\tilde{A}(r_S)$ is the cumulated activity in source region r_S, and $S(r_T \leftarrow r_S)$ is the mean absorbed dose to target region r_T per unit cumulated activity in r_S. Hence, the mean absorbed dose to a bone compartment (i.e., bone volume or endosteum) from a radiopharmaceutical distributed in both the bone and bone marrow can be written as:

$$\bar{D}(\text{bone}) = \tilde{A}(\text{bone})\, S(\text{bone} \leftarrow \text{bone}) + \tilde{A}(\text{marrow})\, S(\text{bone} \leftarrow \text{marrow}). \qquad \text{Eq. 2}$$

Similarly, the mean absorbed dose to the bone marrow from radioactivity distributed in these same bone and marrow compartments is given as:

$$\bar{D}(\text{marrow}) = \tilde{A}(\text{bone})\, S(\text{marrow} \leftarrow \text{bone}) + \tilde{A}(\text{marrow})\, S(\text{marrow} \leftarrow \text{marrow}). \qquad \text{Eq. 3}$$

In the palliation of bone pain, the goal is to maximize the absorbed dose to the bone compartment and minimize the absorbed dose to the bone marrow. Consequently, the ratio of the absorbed dose to the bone compartment compared with the dose to the bone marrow is of interest:

$$\frac{\bar{D}(\text{bone})}{\bar{D}(\text{marrow})} = \frac{\tilde{A}(\text{bone})\, S(\text{bone} \leftarrow \text{bone}) + \tilde{A}(\text{marrow})\, S(\text{bone} \leftarrow \text{marrow})}{\tilde{A}(\text{bone})\, S(\text{marrow} \leftarrow \text{bone}) + \tilde{A}(\text{marrow})\, S(\text{marrow} \leftarrow \text{marrow})}. \qquad \text{Eq. 4}$$

Generally, for bone-seeking radiopharmaceuticals, the cross-dose to the marrow and bone from all other sources of activity in the body (e.g., muscle, kidney) is small compared with the contributions from activity in the marrow and bone and may therefore be ignored in these estimates. Hence, the advantage of test radionuclide T compared with reference radionuclide R for palliation of bone pain may be expressed as a dosimetric RAF:

$$\text{RAF} = \frac{\dfrac{\bar{D}_T(\text{bone})}{\bar{D}_T(\text{marrow})}}{\dfrac{\bar{D}_R(\text{bone})}{\bar{D}_R(\text{marrow})}} = \frac{\bar{D}_T(\text{bone})}{\bar{D}_T(\text{marrow})} \times \frac{\bar{D}_R(\text{marrow})}{\bar{D}_R(\text{bone})}, \text{ and}$$

$$\text{RAF} = \frac{\tilde{A}_T(B)S_T(B \leftarrow B) + \tilde{A}_T(M)S_T(B \leftarrow M)}{\tilde{A}_T(B)S_T(M \leftarrow B) + \tilde{A}_T(M)S_T(M \leftarrow M)} \times \frac{\tilde{A}_R(B)S_R(M \leftarrow B) + \tilde{A}_R(M)S_R(M \leftarrow M)}{\tilde{A}_R(B)S_R(B \leftarrow B) + \tilde{A}_R(M)S_R(B \leftarrow M)}, \qquad \text{Eq. 5}$$

where the letters B and M denote bone and marrow, respectively. This last equation can be further simplified by using ratios of cumulated activity in bone and marrow compartments for both the reference and test radiopharmaceuticals:

$$\text{RAF} = \frac{\alpha_T S_T(B \leftarrow B) + S_T(B \leftarrow M)}{\alpha_T S_T(M \leftarrow B) + S_T(M \leftarrow M)} \times \frac{\alpha_R S_R(M \leftarrow B) + S_R(M \leftarrow M)}{\alpha_R S_R(B \leftarrow B) + S_R(B \leftarrow M)}, \qquad \text{Eq. 6}$$

where α_T and α_R are the ratios of the cumulated activity in the bone relative to cumulated activity in the marrow for the test and reference radiochemicals, respectively:

$$\alpha_T = \frac{\tilde{A}_T(B)}{\tilde{A}_T(M)} \quad \text{and} \quad \alpha_R = \frac{\tilde{A}_R(B)}{\tilde{A}_R(M)}. \qquad \text{Eq. 7}$$

Average Skeletal S Values for Human Trabecular Bone

The S values for sources and targets in trabecular bone of the human skeleton are taken from Bouchet et al. (*11*) and are summarized in Table 2. The S values represent a weighted skeletal average over 22 trabecular bone regions (13 containing active marrow) of a 70-kg standard man including cranium, mandible,

TABLE 2
Skeletal Average S Values* for Human Trabecular Bone (mGy/MBq/s)

Source region	Target region	^{32}P	^{33}P	^{89}Sr	^{117m}Sn	^{153}Sm	^{169}Er	^{177}Lu	^{186}Re
Active marrow	Active marrow	6.58E-05	9.57E-06	5.58E-05	1.88E-05	2.97E-05	1.24E-05	1.69E-05	3.50E-05
Active marrow	Bone endosteum	7.63E-05	4.83E-06	6.33E-05	1.06E-05	2.28E-05	7.15E-06	1.15E-05	3.46E-05
Active marrow	Bone volume	3.30E-05	1.22E-06	2.71E-05	2.99E-06	8.46E-06	2.20E-06	3.91E-06	1.41E-05
Bone endosteum	Active marrow	2.45E-05	1.82E-06	2.04E-05	3.88E-06	7.85E-06	2.61E-06	4.07E-06	1.14E-05
Bone endosteum	Bone endosteum	8.87E-05	2.49E-05	7.66E-05	3.81E-05	6.54E-05	3.21E-05	3.47E-05	5.39E-05
Bone endosteum	Bone volume	3.57E-05	5.35E-06	3.04E-05	1.10E-05	1.61E-05	6.82E-06	9.62E-06	1.94E-05
Bone volume	Active marrow	2.26E-05	7.69E-07	1.86E-05	1.89E-06	5.64E-06	1.41E-06	2.55E-06	9.59E-06
Bone volume	Bone endosteum	8.44E-05	9.03E-06	7.14E-05	1.98E-05	3.25E-05	1.25E-05	1.85E-05	4.34E-05
Bone volume	Bone volume	4.20E-05	1.02E-05	3.66E-05	1.92E-05	2.63E-05	1.25E-05	1.60E-05	2.62E-05

*Mean absorbed dose to target region in trabecular bone per unit cumulated activity in source region.
Data are abstracted from Bouchet et al. (*11*).

humerus (upper and lower half), radius, ulna, hands, scapulae, clavicles, sternum, ribs, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, sacrum, os coxae, and femur (upper and lower half). Details of the Monte Carlo dosimetry model for trabecular bone (*12*) and details of the S value determinations (*11*) have been reported elsewhere. Briefly, the electron transport through the 3-dimensional microstructure of human trabecular bone was simulated by sampling chord-length distributions through bone trabeculae and marrow cavities measured by Beddoe et al. (*13*) (*14–17*). Using the EGS4/PRESTA Monte Carlo transport code (*18–20*) to simulate the physics of electron transport, absorbed fractions of energy were calculated for 3 source–target regions: the trabecular marrow space (TMS), the trabecular endosteum (TBE), and the trabecular bone volume (TBV). S values were subsequently derived for the 22 bone sites, using standard masses derived from reference data (*21*), and for all trabecular regions used in the calculations of the absorbed fraction. In addition, explicit consideration of the trabecular active marrow (TAM) as both a source and target region was made. Corresponding skeletal averages of these regional S values were also calculated as discussed in Bouchet et al. (*11*). The skeletal average S values for human trabecular bone, summarized in Table 2, were used below to ascertain the relative dosimetric merits of various radiochemicals for palliation of bone pain.

RESULTS

The average skeletal S values for human trabecular bone given in Table 2 were used in Equation 6 to calculate RAFs for several radiopharmaceuticals tagged with the radionuclides ^{32}P, ^{89}Sr, ^{186}Re, ^{153}Sm, ^{177}Lu, ^{169}Er, ^{117m}Sn, or ^{33}P. RAFs were calculated for 2 different source regions, the endosteum and bone volume of trabecular bone. These source regions correspond to those observed for various radiopharmaceuticals that use the radionuclides listed in Table 1. The bone volume was taken as the relevant target region (*22*). For each source region, 2 different values of cumulated activity ratios were assumed, $\alpha = 10$ and $\alpha = 100$, corresponding to a cumulated activity in the bone 10 or 100 times larger than that found in the marrow.

When the endosteum was taken as the source region and bone volume was taken as the target region, the RAF values given in Table 3 were obtained. These RAF values allowed an intercomparison among all of the radiopharmaceuticals: an RAF value less than unity corresponds to the test radiopharmaceutical with characteristics less advantageous than the reference radiopharmaceutical for alleviating bone pain. On the other hand, a value of RAF greater than unity corresponds to a test radiopharmaceutical with characteristics more advantageous than the reference radiochemical for alleviating bone pain. When the bone volume was taken as both source and target the RAF values given in Table 4 were obtained.

As expected, for both surface- and volume-seeking radiopharmaceuticals, the largest values of RAF were obtained when the cumulated activity ratio for the test radiochemical was greater than for the reference radiochemical ($\alpha_T = 100$ and $\alpha_R = 10$). For these two ratios, RAF's ranged as high as 2.2 and 7.3 when the endosteum and the bone volume were the assumed source regions, respectively. These maximum values of RAF were calculated when the energetic β-emitter ^{32}P and the low-energy β-emitter ^{33}P were compared.

For the radionuclides examined in these calculations, the order of preference in terms of their capacity to irradiate bone while sparing marrow was independent of the cumulated activity ratios and was ^{33}P, ^{117m}Sn, ^{169}Er, ^{177}Lu, ^{153}Sm, ^{186}Re, ^{89}Sr, and ^{32}P. As expected, the radionuclides were in order of ascending mean particle emission energy (Table 1). By comparing equivalent entries within Tables 3 and 4, the model can be used to predict an efficacy for radiopharmaceuticals tagged with either ^{32}P or ^{89}Sr that is essentially the same, regardless of how the radioactivity is distributed within the bone tissue.

DISCUSSION

Limitations in S Values

S values used to calculate the RAF for the different radionuclides of Table 1 were calculated for only the electron component of the disintegration (*11*). Indeed, in the model of electron transport used in this study (*12*), the path of the transported particles was assumed to be small compared

TABLE 3
Dosimetric RAFs for Endosteum Source and Bone Volume Target for 2 Ratios of Cumulated Activity in Bone Versus Marrow

α_T = 10 and α_R = 100

Test radionuclide	Reference radionuclide							
	^{32}P	^{89}Sr	^{186}Re	^{153}Sm	^{177}Lu	^{169}Er	^{117m}Sn	^{33}P
^{32}P	0.9							
^{89}Sr	0.9	0.9						
^{186}Re	1.0	1.0	0.8					
^{153}Sm	1.1	1.1	0.9	0.8				
^{177}Lu	1.2	1.2	1.0	0.9	0.8			
^{169}Er	1.3	1.2	1.1	0.9	0.8	0.7		
^{117m}Sn	1.4	1.3	1.2	1.0	0.9	0.8	0.7	
^{33}P	1.4	1.3	1.2	1.0	0.9	0.8	0.7	0.7

α_T = 10 and α_R = 10

Test radionuclide	Reference radionuclide							
	^{32}P	^{89}Sr	^{186}Re	^{153}Sm	^{177}Lu	^{169}Er	^{117m}Sn	^{33}P
^{32}P	1.0							
^{89}Sr	1.0	1.0						
^{186}Re	1.1	1.1	1.0					
^{153}Sm	1.2	1.2	1.1	1.0				
^{177}Lu	1.4	1.4	1.2	1.1	1.0			
^{169}Er	1.5	1.4	1.3	1.2	1.1	1.0		
^{117m}Sn	1.6	1.5	1.4	1.3	1.1	1.1	1.0	
^{33}P	1.6	1.5	1.4	1.3	1.1	1.1	1.0	1.0

α_T = 100 and α_R = 100

Test radionuclide	Reference radionuclide							
	^{32}P	^{89}Sr	^{186}Re	^{153}Sm	^{177}Lu	^{169}Er	^{117m}Sn	^{33}P
^{32}P	1.0							
^{89}Sr	1.0	1.0						
^{186}Re	1.2	1.1	1.0					
^{153}Sm	1.4	1.4	1.2	1.0				
^{177}Lu	1.6	1.6	1.4	1.1	1.0			
^{169}Er	1.7	1.7	1.5	1.3	1.1	1.0		
^{117m}Sn	1.9	1.9	1.6	1.4	1.2	1.1	1.0	
^{33}P	2.0	1.9	1.7	1.4	1.2	1.1	1.0	1.0

α_T = 100 and α_R = 10

Test radionuclide	Reference radionuclide							
	^{32}P	^{89}Sr	^{186}Re	^{153}Sm	^{177}Lu	^{169}Er	^{117m}Sn	^{33}P
^{32}P	1.1							
^{89}Sr	1.2	1.1						
^{186}Re	1.3	1.3	1.2					
^{153}Sm	1.6	1.6	1.4	1.3				
^{177}Lu	1.8	1.8	1.6	1.5	1.3			
^{169}Er	2.0	2.0	1.8	1.6	1.4	1.4		
^{117m}Sn	2.2	2.1	1.9	1.7	1.6	1.5	1.4	
^{33}P	2.2	2.2	2.0	1.8	1.6	1.5	1.4	1.4

TABLE 4
Dosimetric RAFs for Bone Volume Source and Bone Volume Target for 2 Ratios of Cumulated Activity in Bone Versus Marrow

α_T = 10 and α_R = 100

Test radionuclide	Reference radionuclide							
	^{32}P	^{89}Sr	^{186}Re	^{153}Sm	^{177}Lu	^{169}Er	^{117m}Sn	^{33}P
^{32}P	0.9							
^{89}Sr	0.9	0.8						
^{186}Re	1.2	1.1	0.8					
^{153}Sm	1.7	1.6	1.2	0.7				
^{177}Lu	2.1	2.0	1.5	0.9	0.7			
^{169}Er	2.6	2.5	1.8	1.1	0.8	0.6		
^{117m}Sn	2.8	2.7	2.0	1.2	0.9	0.6	0.6	
^{33}P	3.3	3.1	2.3	1.3	1.0	0.7	0.6	0.5

α_T = 10 and α_R = 10

Test radionuclide	Reference radionuclide							
	^{32}P	^{89}Sr	^{186}Re	^{153}Sm	^{177}Lu	^{169}Er	^{117m}Sn	^{33}P
^{32}P	1.0							
^{89}Sr	1.0	1.0						
^{186}Re	1.4	1.3	1.0					
^{153}Sm	2.0	1.9	1.5	1.0				
^{177}Lu	2.5	2.4	1.8	1.2	1.0			
^{169}Er	3.1	3.0	2.3	1.5	1.2	1.0		
^{117m}Sn	3.3	3.2	2.5	1.6	1.3	1.1	1.0	
^{33}P	3.9	3.7	2.8	1.9	1.5	1.2	1.2	1.0

α_T = 100 and α_R = 100

Test radionuclide	Reference radionuclide							
	^{32}P	^{89}Sr	^{186}Re	^{153}Sm	^{177}Lu	^{169}Er	^{117m}Sn	^{33}P
^{32}P	1.0							
^{89}Sr	1.1	1.0						
^{186}Re	1.5	1.4	1.0					
^{153}Sm	2.4	2.3	1.7	1.0				
^{177}Lu	3.2	3.1	2.2	1.3	1.0			
^{169}Er	4.5	4.2	3.1	1.8	1.4	1.0		
^{117m}Sn	5.1	4.8	3.5	2.1	1.6	1.1	1.0	
^{33}P	6.5	6.1	4.5	2.7	2.0	1.4	1.3	1.0

α_T = 100 and α_R = 10

Test radionuclide	Reference radionuclide							
	^{32}P	^{89}Sr	^{186}Re	^{153}Sm	^{177}Lu	^{169}Er	^{117m}Sn	^{33}P
^{32}P	1.2							
^{89}Sr	1.2	1.2						
^{186}Re	1.7	1.6	1.3					
^{153}Sm	2.9	2.7	2.1	1.4				
^{177}Lu	3.8	3.6	2.8	1.9	1.5			
^{169}Er	5.3	5.0	3.9	2.6	2.1	1.7		
^{117m}Sn	6.0	5.7	4.4	2.9	2.4	1.9	1.8	
^{33}P	7.6	7.3	5.6	3.7	3.1	2.5	2.3	2.0

with the macroscopic dimensions of the bone. Consequently, in the calculations of S values for the radionuclides considered in a previous study (*11*), the photon component (x and γ rays) was assumed to be negligible compared with the electron component. For pure β emitters (^{32}P, ^{89}Sr, and ^{33}P) and for radionuclides with small photon emission components (^{169}Er and ^{186}Re), these S values were consequently adequate. However, for ^{117m}Sn, ^{153}Sm, and ^{177}Lu, the electron and photon component of the mean energy emitted per transition were of the same order of magnitude. To evaluate the error due to exclusion of the photon component in the S value calculations, photon-specific absorbed fractions of

energy from MIRD calculations (*23*) can be used. These photon-specific absorbed fractions were derived using a homogenized skeletal mixture, and the absorbed fractions were partitioned by mass ratios (*24*). Consequently, these specific absorbed fractions of energy were overestimated when the marrow was considered the target region and underestimated when the bone was considered the target region (*23*).

Source and target regions of interest for the RAF calculations were the red marrow and the bone volume. MIRD photon-specific absorbed fractions of energy are given for the red marrow, yellow marrow, and the skeleton as source regions, and the red marrow and bone volume as target regions (*23*). Using these data, S value contributions from the emitted photon radiation of the decay were estimated for ^{117m}Sn, ^{153}Sm, and ^{177}Lu. As expected, the maximum errors in the S value were seen when the bone volume and red marrow were used as either the source or target region. For these 2 source–target combinations, the error in the S value for ^{153}Sm and ^{177}Lu was <5% and <20% for ^{117m}Sn (10% when the red marrow is the source and 20% when the bone was the source). Errors in the S values when the source and target regions are the same was <5% for all 3 radionuclides. RAFs calculated using S values that considered the x-ray/γ-ray component of the decay scheme did not change for either ^{153}Sm or ^{177}Lu. Only a 10% decrease was noted in the RAFs for ^{117m}Sn. Consequently, the RAF calculated using S values that did not account for the photons could be considered valid for all radionuclides considered in Table 1.

Limitations in RAF Calculations

The RAF results presented in Tables 3 and 4 suggest that radionuclides that emit short-range electrons/β-particles offer a distinct advantage over energetic β-particle emitters in the palliation of bone pain caused by osseous metastases. RAFs ranging as high as ~6 were obtained for the lowest energy emitter ^{33}P when compared with the energetic β emitter ^{32}P (α = 100). These theoretical RAF calculations used a model that considers only normal bone and normal marrow. Not considered is the impact of abnormal bone, which has different architecture and much higher uptake of radioactivity than surrounding normal bone. Therefore, the RAFs reported here may be taken as lower estimates of the true RAF, given that higher absorbed doses will be delivered to metastatic lesions (*25*).

There are other factors that have not been folded into these calculations that may affect the overall relative advantage of one radionuclide compared to another. Among the many potential factors not considered in the present model are the physical half-life of the radionuclide, the microscopic distribution of the radiochemical, the fraction of injected activity taken up by bone, the kinetics of the radiochemical in bone tissue, as well as the cost and availability of the radionuclide. For example, the physical half-life affects the injected activity required, as well as the duration of pain relief. Longer-lived radionuclides generally require lower injected activities and show more prolonged pain relief; however, they also are slower acting in terms of the initial reduction in pain (*22*). This may be the result of the lower dose rates delivered by these radionuclides. In addition, they may lengthen the time required between injections when bone marrow toxicity is an issue. Such issues may also need to be considered when selecting the optimal radionuclide for palliation of bone pain.

Variation of RAF with Cumulated Activity Ratio

It is interesting to analyze variations of the RAFs with cumulated activity ratios. Tables 3 and 4 also give RAF values for test and reference radiochemicals labeled with the same radionuclide but with cumulated activity ratios of 100 and 10, respectively. This scenario represents a comparison of 2 different radiopharmaceuticals labeled with the same radionuclide. For the high-energy β emitters such as ^{32}P and ^{89}Sr, an increase by a factor of 10 in the cumulated activity ratio increases the RAF by only ~10% and ~20% for endosteum and volume sources, respectively. On the other hand, for the low-energy β emitters ^{117m}Sn and ^{33}P, the corresponding increase is ~40% and ~90%, respectively. Therefore, an increase in cumulated activity ratios between bone volume and marrow is dosimetrically more significant for the low-energy β emitters than for high-energy β emitters. Furthermore, an increase in the cumulated activity ratio leads to a larger RAF when the radiochemical concentrates in the bone volume versus the bone endosteum.

RAF for ^{117m}Sn-DTPA, ^{153}Sm-EDTMP, and ^{33}P-Orthophosphate

Radionuclides such as ^{117m}Sn and ^{33}P can offer a significant advantage over ^{153}Sm, the radionuclide that was recently approved by the FDA for alleviation of bone pain. Although the advantage is relatively small (RAF < 1.8) when the endosteum is taken as the source and bone volume is taken as the target (Table 3), it is substantial (RAF < 3.7) when the bone volume is taken as both the source and target (Table 4). Given that ^{117m}Sn-diethylenetriamine pentaacetic acid (DTPA) and ^{153}Sm-EDTMP are known to localize almost exclusively on bone surfaces and a substantial fraction of ^{33}P-orthophosphate localizes in the bone volume (*26,27*), perhaps the most useful comparison among these 3 radionuclides would take into account differences in biodistribution. Using the skeletal S values in Table 2 and the definition of the RAF given by Equation 6, and assuming a cumulative activity ratio of 100 for both the test and reference radiochemicals, the relative dosimetric advantage of ^{33}P-orthophosphate over ^{153}Sm-EDTMP can be calculated to be 5.9, when ^{33}P and ^{153}Sm are distributed in the bone volume and endosteum, respectively. This is compared with an RAF of only 1.4 between the surface seekers ^{117m}Sn-DTPA and ^{153}Sm-EDTMP (Table 3, $\alpha_T = \alpha_R = 100$). An RAF of 4.4 is obtained when ^{33}P-orthophosphate is similarly compared with ^{117m}Sn-DTPA. Therefore, based on theoretical dosimetric considerations only, ^{33}P-orthophosphate seems to be an excellent choice for palliation of bone pain resulting from osseous metastases. This radionuclide was previously

suggested as a potential candidate by Potsaid et al. (*3*), when they found that ^{32}P caused marrow toxicity regardless of its radiochemical form. Our experiments in laboratory mice using intravenously administered ^{32}P and ^{33}P indeed show that for a given absorbed dose to the bone, the survival of granulocyte/macrophage colony forming cells (GM-CFC) in the femoral marrow is considerably higher with ^{33}P than with ^{32}P (*28*). Given that GM-CFC survival is an indication of marrow toxicity, this suggests that ^{33}P offers a distinct therapeutic advantage. There are some drawbacks to this radionuclide, among them the high muscle uptake (*28*), the absence of imaging photons, and the high injected activities that may be required as a result of the low energy of the emitted β particles. These drawbacks, however, may be offset by the high dosimetric RAFs predicted for this radionuclide.

CONCLUSION

In the treatment of bone pain with radiopharmaceuticals, low-energy electron emitters such as ^{117m}Sn and ^{33}P are preferred because they are more likely to deliver a therapeutic dose to the bone and spare the bone marrow than are energetic β emitters such as ^{32}P and ^{89}Sr.

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REFERENCES

1. Silberstein EB. The treatment of painful osseous metastases with phosphorus-32-labeled phosphates. *Semin Oncol.* 1993;20:10–21.
2. Ackery D, Yardley J. Radionuclide-targeted therapy for the management of metastatic bone pain. *Semin Oncol.* 1993;20(3 suppl 2):27–31.
3. Potsaid MS, Irwin RJ Jr, Castronovo FP, et al. [^{32}P] diphosphonate dose determination in patients with bone metastases from prostatic carcinoma. *J Nucl Med.* 1978;19:98–104.
4. Holmes RA. Radiopharmaceuticals in clinical trials. *Semin Oncol.* 1993;20:22–26.
5. Ketring AR. ^{153}Sm-EDTMP and ^{186}Re-HEDP as bone therapeutic radiopharmaceuticals. *Int J Rad Appl Instrum [B].* 1987;14:223–232.
6. Collins C, Eary JF, Donaldson G, et al. Samarium-153-EDTMP in bone metastases of hormone refractory prostate carcinoma: a phase I/II trial. *J Nucl Med.* 1993;34:1839–1844.
7. Atkins HL, Mausner LF, Srivastava SC, Meinken GE, Cabahug CJ, D'Alessandro T. Tin-117m(4+)-DTPA for palliation of pain from osseous metastases: a pilot study. *J Nucl Med.* 1995;36:725–729.
8. Swailem FM, Krishnamurthy GT, Srivastava SC, et al. In-vivo tissue uptake and retention of Sn-117m(4+)DTPA in a human subject with metastatic bone pain and in normal mice. *Nucl Med Biol.* 1998;25:279–287.
9. Krishnamurthy GT, Swailem FM, Srivastava SC, et al. Tin-117m(4+)DTPA: pharmacokinetics and imaging characteristics in patients with metastatic bone pain. *J Nucl Med.* 1997;38:230–237.
10. Loevinger R, Budinger TF, Watson EE. *MIRD Primer for Absorbed Dose Calculations.* Revised ed. New York, NY: The Society of Nuclear Medicine; 1991.
11. Bouchet LG, Bolch WE, Howell RW, Rao DV. S values for radionuclides localized within the skeleton. *J Nucl Med.* 2000;41:189–212.
12. Bouchet LG, Jokisch WJ, Bolch WE. A three-dimensional transport model for determining absorbed fractions of energy for electrons within trabecular bone. *J Nucl Med.* 1999;40:1947–1966.
13. Beddoe AH, Darley PJ, Spiers FW. Measurements of trabecular bone structure in man. *Phys Med Biol.* 1976;21:589–607.
14. Beddoe AH. Measurements of the microscopic structure of cortical bone. *Phys Med Biol.* 1977;22:298–308.
15. Darley PJ. *An Investigation of the Structure of Trabecular Bone in Relation to the Radiation Dosimetry of Bone-Seeking Radionuclides* [thesis]. Leeds, UK: University of Leeds; 1972.
16. Whitwell JR. *Theoretical Investigations of Energy Loss by Ionizing Particles in Bone* [thesis]. Leeds, UK: University of Leeds; 1973.
17. Whitwell JR, Spiers FW. Calculated beta-ray dose factors for trabecular bone. *Phys Med Biol.* 1976;21:16–38.
18. Bielajew AF, Rogers DWO. PRESTA, the "parameter reduced electron step transport algorithm" for electron Monte Carlo transport. *Nucl Instr Meth B.* 1987;18:165–181.
19. Ford RL, Nelson WR. *The EGS Code System: Computer Programs for Monte Carlo Simulation of Electromagnetic Cascade Shower.* Report 210. Palo Alto, CA: Stanford Linear Accelerator Center; 1978.
20. Nelson WR, Hirayama RH, Roger DWO. *The EGS4 Code System.* SLAC-Report-265. Palo Alto, CA: Stanford Linear Accelerator Center; 1985.
21. International Commission on Radiological Protection. *Basic Anatomical and Physiological Data for Use in Radiological Protection: The Skeleton.* ICRP Publication 70. Tarrytown, NY: International Commission on Radiological Protection; 1995.
22. Lewington VJ. Cancer therapy using bone-seeking isotopes. *Phys Med Biol.* 1996;41:2027–2042.
23. Snyder WS, Ford MR, Warner GG. *Estimates of Specific Absorbed Fractions for Photon Sources Uniformly Distributed in Various Organs of a Heterogeneous Phantom.* MIRD Pamphlet No. 5, revised. New York, NY: Society of Nuclear Medicine; 1978.
24. Snyder WS, Ford MR, Warner GG, Watson SB. *A Tabulation of Dose Equivalent per Microcurie-Day for Source and Target Organs of an Adult for Various Radionuclides.* ORNL-5000. Oak Ridge, TN: Oak Ridge National Laboratory; 1974.
25. Samaratunga RC, Thomas SR, Hinnefeld JD, et al. A Monte Carlo simulation model for radiation dose to metastatic skeletal tumor from rhenium-186(Sn)-HEDP. *J Nucl Med.* 1995;36:336–350.
26. Leblond CP, Wilkinson GW, Belanger LF, Robichon J. Radio-autographic visualization of bone formation in the rat. *Am J Anat.* 1950;9:289–296.
27. Leblond CP, Wilkinson GW, Belanger LF, Robichon J. Radio-autographic visualization of bone formation in the rat. *J NIH Res.* 1997;9:44–55.
28. Goddu SM, Bishayee A, Bouchet LG, Bolch WE, Rao DV, Howell RW. Marrow toxicity of ^{33}P- versus ^{32}P-orthophosphate: implications for therapy of bone pain and bone metastases. *J Nucl Med.* 2000: in press.
29. Brown E, Firestone RB. *Table of Radioactive Isotopes.* New York, NY: Wiley; 1986.
30. Weber DA, Eckerman KF, Dillman LT, Ryman JC. *MIRD: Radionuclide Data and Decay Schemes.* New York, NY: Society of Nuclear Medicine; 1989.
31. International Commission on Radiation Units and Measurements. *Stopping Powers for Electrons and Positrons.* ICRU Report 37. Bethesda, MD: International Commission on Radiation Units and Measurements; 1984.