Radiopharmaceuticals for Bone Malignancy Therapy

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Objective: This continuing education article reviews radionuclide bone therapy agents that are available commercially and introduces agents that are being evaluated for future use. Currently these agents are used to provide pain palliation from metastases to bone. Future applications may include adjuvant therapy to surgery or external beam treatment. After reading this paper, the reader should be able to: (a) describe the desirable characteristics of radionuclide bone therapy agents; (b) compare and contrast radiopharmaceuticals available for bone therapy; and (c) state the clinical applications of radionuclide bone therapy agents.

Key Words: cancer; radionuclide therapy of bone malignancies; palliation from metastases to bone; strontium-89; phosphorus-32; tin-117m; rhenium-186; samarium-153

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Throughout most of the history of nuclear medicine, the emphasis has been on diagnostic applications. A major exception has been the treatment of benign and malignant thyroid disease with ^{131}I. Hematologic disease also has received some attention with the use of ^{32}P. Recently there has been increased interest in using various labeled compounds for the therapy of malignancy. Some of these compounds include labeled monoclonal antibodies and other receptor-avid molecules.

The interest in applying radionuclides to therapy of bone malignancies, particularly for palliative relief of bone pain, has been renewed. This interest had its origin in the earliest days of the nuclear era but fell into relative obscurity for some time until recently. Both ^{89}Sr and ^{32}P were investigated as early as the 1940s for treating metastatic cancer to bone (*1,2*). The work of Firusian (*3*) suggested again that ^{89}Sr would be useful for relief of pain secondary to osseous metastases. Robinson and others further explored the use of ^{89}Sr (*4–7*) resulting in the FDA approval for its routine application in 1993. This work also has stimulated clinical research to find other radionuclides that may have improved physical properties that permit treatment with fewer side effects on the myeloproliferative cells in the bone marrow. This paper compares several agents that may be useful in treating bone malignancy and discusses possible ways in which these agents may be applied to provide increased benefits to patients.

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DESIRED CHARACTERISTICS OF BONE THERAPY AGENTS

Half-Life

The half-life ($T_{1/2}$) of a radionuclide determines the initial dose rate and, therefore, the total amount of radioactivity to be administered. What constitutes an appropriate physical $T_{1/2}$ is not well understood. A higher initial dose rate may result in more effective cell killing, but the therapeutic ratio of malignant cell destruction to normal cell recovery may be less. Too long a $T_{1/2}$ creates obvious problems in environmental safety in case of spill or early death of the patient. A very short $T_{1/2}$ is problematic so far as shipping and shelf life are concerned. It also requires a larger total of administered activity which increases the radiation dose to personnel and family members and may require some hospitalization, thus increasing cost. On the other hand, repetitive doses may be given at shorter intervals making it possible to titrate dose to response.

Photon Emission

The accompanying photon emissions of the appropriate energy can be useful in monitoring the distribution of the radiopharmaceutical in the patient to assess dosimetry, but are not essential. They also constitute a source of exposure to personnel and family, but this has not been a significant problem with the radionuclides investigated to date.

Electron Emission

Both ^{89}Sr and ^{32}P, the earliest radionuclides used for bone malignancy therapy, have highly energetic beta emissions. These penetrate deeply into the marrow cavity and may be the cause of increased myelotoxicity. More recent research has concentrated on radionuclides that have much lower energy electron emissions and, therefore, potentially have reduced toxicity.

Other Factors

Ease of preparation, in vitro and in vivo stability, shelf life and cost are other considerations. Radionuclides that can be

TABLE 1
Radionuclides for Bone Pain Therapy

	Maximum beta energy (MeV)	Average beta energy (MeV)	Average range (mm)	$T_{1/2}$ (days)	Gamma photon (MeV)
^{89}Sr	1.46	0.58	2.4	50.5	None
^{32}P	1.71	0.70	3.0	14.3	None
^{117m}Sn	0.13*	—	0.22	14.0	0.159 (86%)
	0.15*	—	0.29		
^{186}Re	1.08	0.33	1.05	3.7	0.137 (9%)
^{153}Sm	0.81	0.22	0.55	1.9	0.103 (29%)

*Conversion electrons with discrete energies (and range).

prepared in a reactor are usually less costly. Ease of preparation and cost are dependent on the nuclear reactions and subsequent radiochemical processing required for manufacture.

COMPARISON OF RADIOPHARMACEUTICALS

The relevant physical characteristics of the various radionuclides are given in Table 1. As of this writing, ^{89}Sr-chloride (Metastron, Amersham Healthcare/Medi-Physics, Arlington Heights, IL) and ^{153}Sm EDTMP (Quadramet, DuPont Pharma, North Billerica, MA) have been approved by the FDA. Phosphorus-32 as sodium phosphate was grandfathered in as an approved drug when the FDA took over jurisdiction of radiopharmaceuticals from the Atomic Energy Commission. Rhenium-186 (and ^{188}Re) HEDP and ^{117m}Sn stannic DTPA are still under investigation.

Strontium-89-Chloride

Strontium-89 is a pure beta emitter. The maximum beta energy is high and penetration is average, at 2.4 mm, in soft tissue. The long physical $T_{1/2}$ means that low administered activity is given, resulting in a rather low initial dose rate. In addition, it limits the possibility of repeat doses until much after the initial dosing. Nevertheless, it has proven effective (*6–9*). Absence of an accompanying gamma photon makes it difficult, but not impossible, to monitor distribution. The energetic betas result in a low bone-to-marrow dose ratio but myelotoxicity has not been a major factor. While individual studies vary in results, the overall efficacy in terms of patients experiencing pain relief (complete + marked + moderate) appears to be in the range of 54% (*9*) to 80% (*7*).

Phosphorus-32-Phosphate

Phosphorus-32 is taken up also by soft tissues which undergo rapid cell division, such as in the bowel lining and the bone marrow itself in addition to involved bone. Therefore, the bone-to-marrow ratio is low. Similar to ^{89}Sr, ^{32}P has a highly energetic beta emission, and has no accompanying gamma photon making monitoring somewhat difficult. Results have been similar to ^{89}Sr, but toxicity to the bone marrow has been severe at times (*10–12*). Due to this reason, its use is not favored at the present time.

Samarium-153 EDTMP

Samarium-153 EDTMP has a short physical $T_{1/2}$ of 1.9 days. This can be advantageous in that it is easier to administer repeated doses. However, it makes manufacturing and delivery a more difficult problem. The range of its beta particles is short (average 0.55 mm) resulting in good bone-to-marrow ratios ranging between 2 and 5.5. Myelotoxicity has been manageable at the approved dose schedule (1 mCi/kg), and efficacy is in a similar range as ^{89}Sr (*13–16*). At high levels of administered ^{153}Sm, an increase in survival of patients with metastatic prostate cancer was demonstrated, but at the cost of severe myelotoxicity (*15*).

Rhenium-186 HEDP

The physical $T_{1/2}$ of ^{186}Re is 3.7 days. This is long enough that shipment and shelf life are less of a problem than with ^{153}Sm. It is short enough that repeated doses can be given over a relatively short period of time. However, the average beta energy is considerably higher than that of ^{153}Sm, and consequently the range is longer so that, at least theoretically, it is less sparing of the bone marrow. The dose ratio of bone-to-marrow is not particularly favorable and the compound is less stable than the other radiopharmaceuticals under discussion (*17,18*).

TABLE 2
Dosimetry of Bone Agents*

	Radiation dose (rad/mCi)		
	Bone surfaces	Red marrow	Bone/Marrow dose ratio
$^{89}Sr\ Cl_2$	63.0	40.7	1.6
^{186}Re HEDP	7.0	3.0	2.3
^{153}Sm EDTMP	15.4	2.8	5.5
^{117m}Sn DTPA	65.1	9.8	6.6

*Data from reference *21*.

TABLE 3
Myelotoxicity Levels*

Radiopharmaceutical	Dose group (mCi/Kg)	n	No. of patients with grade ≥ 2		Reference no.
			WBC	Platelets	
$^{89}Sr\ Cl_2$	0.154	67	25 (37%)	41 (61%)	(24)
	0.040	161	[48 (31%)**]	—	(27)
^{186}Re HEDP	0.500–1.143	12	2 (17%)	3 (25%)	(28)
^{153}Sm EDTMP	1.00	20	3 (15%)	5 (25%)	(29)
	1.50	4	3 (75%)	1 (25%)	
	3.00	4	4 (100%)	2 (50%)	
^{117m}Sn DTPA	0.143	9	1 (11%)	0 (0%)	(22)
	0.179	5	0 (0%)	0 (0%)	
	0.286	12	1 (8%)	0 (0%)	

*Using NCI criteria.

**Only "hematological toxicity" grade ≥ 2 mentioned.

Tin-117m Stannic DTPA

At this time only limited clinical experience has been obtained with ^{117m}Sn stannic DTPA (*19–22*). Its physical characteristics are very favorable. The range of the electron emission (monoenergetic conversion electrons) is less than that of any of the other compounds so that the radiation absorbed dose to the marrow is considerably less, giving the best bone-to-marrow ratio (Table 2). The initial dose rate is higher than that obtained with ^{89}Sr and the $T_{1/2}$ is ideal so far as shipment and shelf life are concerned. Its in vitro and in vivo stability are very high (*23*). An accompanying gamma photon is useful for monitoring. Results so far indicate a very low myelotoxicity (Table 3) and the efficacy is similar to the other compounds (*22*).

CLINICAL APPLICATIONS

The compounds discussed above have been considered primarily as agents to provide pain palliation in far advanced metastases involving bone. The requirements for achieving this purpose are rather modest. It is not necessary to obtain much tumor regression and it is desirable to avoid significant toxicity. Therefore, for achieving pain palliation, it is not necessary to administer the highest doses possible.

However, there are hints that more than just pain palliation can be achieved in the appropriate clinical situation. Our data indicate that an earlier onset of response occurs with higher levels of administered ^{117m}Sn activity (*22*). The Trans-Canada Study performed with high doses of ^{89}Sr in patients with relatively early metastatic disease of the prostate demonstrated that, as an adjuvant to external beam treatment, the interval to new painful metastases could be significantly lengthened (*24*). In addition, others have demonstrated reversal of changes on the radionuclide bone imaging study with ^{89}Sr (*25*). Radiographs after radionuclide therapy have shown healing of lytic metastases (*2,26*) thus demonstrating that tumor regression actually can occur. It also has been shown that treating earlier disease is more successful than treating more advanced disease.

Prolongation of survival has been reported using very high doses (2.5 mCi/kg) of ^{153}Sm EDTMP (*15*). This has been attained at the expense of increased morbidity as evidenced by a greater increase in myelotoxicity.

CONCLUSION

On the basis of these findings, it is reasonable to look at these agents in other situations. They may be useful as adjuvant to external beam radiation therapy and chemotherapy. In primary bone malignancy, the use of radionuclide therapy as an adjuvant to surgery may prevent the appearance of metastatic disease. Earlier application of these agents in a prophylactic mode appears warranted. Their ease of administration and relative lack of toxicity present a strong argument for this approach. If higher doses do prove to be advantageous, then that agent with the lowest toxicity should be considered the most appropriate candidate. Tin-117m stannic DTPA appears to be the agent of choice if future studies (an extended Phase II/Phase III clinical trial is underway) continue to demonstrate reduced toxicity as compared to the other agents, in particular ^{89}Sr and ^{153}Sm.

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