Radiopharmaceuticals for Bone Malignancy Therapy

Harold L. Atkins and Suresh C. Srivastava

Medical Department, Brookhaven National Laboratory, Upton, New York

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


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 131I. Hematologic disease also has received some attention with the use of 32P. 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 89Sr and 32P, the earliest radionuclides used for bone malignancy therapy, have been studied extensively in the past. Both 89Sr and 32P have high energy 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 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

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Maximum beta energy (MeV)</th>
<th>Average beta energy (MeV)</th>
<th>Average range (mm)</th>
<th>T1/2 (days)</th>
<th>Gamma photon (MeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>89Sr</td>
<td>1.46</td>
<td>0.58</td>
<td>2.4</td>
<td>50.5</td>
<td>None</td>
</tr>
<tr>
<td>32P</td>
<td>1.71</td>
<td>0.70</td>
<td>3.0</td>
<td>14.3</td>
<td>None</td>
</tr>
<tr>
<td>117mSn</td>
<td>0.13*</td>
<td>—</td>
<td>0.22</td>
<td>14.0</td>
<td>0.159 (86%)</td>
</tr>
<tr>
<td>186Re</td>
<td>1.08</td>
<td>0.33</td>
<td>1.05</td>
<td>3.7</td>
<td>0.137 (99%)</td>
</tr>
<tr>
<td>153Sm</td>
<td>0.81</td>
<td>0.22</td>
<td>0.55</td>
<td>1.9</td>
<td>0.103 (29%)</td>
</tr>
</tbody>
</table>

*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, 89Sr-chloride (Metastron, Amersham Healthcare/Medi-Physics, Arlington Heights, IL) and 153Sm 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 188Re) HEDP and 117mSn 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 T1/2 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 89Sr, 32P has a highly energetic beta emission, and has no accompanying gamma photon making monitoring somewhat difficult. Results have been similar to 89Sr, 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 T1/2 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 89Sr (13–16). At high levels of administered 153Sm, 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 T1/2 of 186Re is 3.7 days. This is long enough that shipment and shelf life are less of a problem than with 153Sm. 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 153Sm, 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

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Bone dose (rad/mCi)</th>
<th>Bone/Marrow dose ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone surfaces</td>
<td>Red marrow</td>
<td></td>
</tr>
<tr>
<td>89Sr Cl₂</td>
<td>63.0</td>
<td>40.7</td>
</tr>
<tr>
<td>186Re HEDP</td>
<td>7.0</td>
<td>3.0</td>
</tr>
<tr>
<td>153Sm EDTMP</td>
<td>15.4</td>
<td>2.8</td>
</tr>
<tr>
<td>117mSn DTPA</td>
<td>65.1</td>
<td>9.8</td>
</tr>
</tbody>
</table>

*Data from reference 21.
TABLE 3
Myelotoxicity Levels*

<table>
<thead>
<tr>
<th>Radiopharmaceutical</th>
<th>Dose group (mCi/Kg)</th>
<th>n</th>
<th>No. of patients with grade ≥ 2</th>
<th>Reference no.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>WBC</td>
<td></td>
</tr>
<tr>
<td>186Re HEDP</td>
<td>0.154</td>
<td>67</td>
<td>25 (37%)</td>
<td>(24)</td>
</tr>
<tr>
<td></td>
<td>0.040</td>
<td>161</td>
<td>[48 (31%)]**</td>
<td>(27)</td>
</tr>
<tr>
<td>153Sm EDTMP</td>
<td>0.500 – 1.143</td>
<td>12</td>
<td>2 (17%)</td>
<td>(28)</td>
</tr>
<tr>
<td></td>
<td>1.00</td>
<td>20</td>
<td>3 (15%)</td>
<td>(29)</td>
</tr>
<tr>
<td></td>
<td>1.50</td>
<td>4</td>
<td>3 (75%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.00</td>
<td>4</td>
<td>4 (100%)</td>
<td></td>
</tr>
<tr>
<td>117mSn DTPA</td>
<td>0.143</td>
<td>9</td>
<td>1 (11%)</td>
<td>(22)</td>
</tr>
<tr>
<td></td>
<td>0.179</td>
<td>5</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.286</td>
<td>12</td>
<td>1 (8%)</td>
<td></td>
</tr>
</tbody>
</table>

*Using NCI criteria.
**Only “hematological toxicity” grade ≥ 2 mentioned.

**Tin-117m Stannic DTPA**

At this time only limited clinical experience has been obtained with 117mSn 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 89Sr and the T1/2 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 117mSn activity (22). The Trans-Canada Study performed with high doses of 89Sr 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 89Sr (25). Radiographs after radionuclide therapy have shown healing of lytic metastases (2,26) thus demonstrating that tumor regression actually can occur. It has also 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 153Sm 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 89Sr and 153Sm.

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