same range as for prostate cancer patients. Thrombocytopenia is the dose-limiting factor. Further studies to evaluate the efficacy of [186]Re-HEDP in patients with painful bone metastases due to breast cancer by placebo controlled studies are warranted.

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EDITORIAL

Dosage and Response in Radiopharmaceutical Therapy of Painful Osseous Metastases

The treatment of pain caused by bone metastases has been a most rewarding aspect of the practice of nuclear medicine for over four decades. The first radiopharmaceutical utilized for this pur-

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pose was ^{32}P as sodium phosphate, given intravenously or, occasionally, orally (1).

Strontium-89 (as the chloride) was rediscovered in the mid-1970s and used in several North American medical centers beginning about 1980 (2,3). During the 1980s, other radiopharmaceuticals were identified that could reduce or relieve the pain of osteoblastic metastases. To be effective in reducing pain from tumor in bone, such radiopharmaceuticals must have a relatively high affinity for reactive

bone, a beta or electron emission of sufficient energy to reach the cells responsible for the pain and sufficiently long physical and biological half lives to deposit damaging or lethal radiation doses in these cells, whether they be the cancer itself or one of several cytokine-secreting cell types which may mediate the production of bone pain. Inherent in this form of internal radiotherapy is some radiation damage to adjacent functioning marrow cells. The relevant radiopharma-

TABLE 1
Radiopharmaceuticals Used for Bone Palliation

Radiopharmaceutical	Physical half-life (days)	Mean beta or electron energy (MeV)	Avg. penetration in soft tissue (mm)	Gamma photopeak (MeV) (% abundance)	Clinical status (supplier)
^{32}P-sodium orthophosphate	14.3	0.7	3.0	None	FDA approved (Mallinckrodt)
^{89}Sr-strontium chloride	50.5	0.58	2.4	0.910 (0.01%)	FDA approved (Amersham)
^{186}Re-rhenium (Sn)-HEDP	3.8	0.35	1.1	0.137 (9%)	Phase III trial (Mallinckrodt)
^{153}Sm-samarium-EDTMP	1.9	0.29	0.8	0.103 (28%)	Phase III trial (Cytogen)
^{117m}Sn-tin-DTPA	13.6	0.15–0.16* 0.13*	0.29 0.21	0.161 (86%)	Phase III trial (Diatech)

*Electrons but not beta.

ceuticals on the market or under IND (Investigational New Drug status) are listed in Table 1.

These radiopharmaceuticals have widely varying half-lives, differing by as much as a factor of 26 (^{89}Sr compared to ^{153}Sm) with a mean particle energy variation from 0.13–0.70 MeV, a ratio exceeding 5 to 1. Yet, the response rates to all of these radiopharmaceuticals have been uniformly reported to be 65%–80% for a wide range of injected dosages or activity ("activity" or "dosage" refer to the amount of radionuclide given in millicuries or becquerels, while the term "dose" refers to the energy absorbed per unit mass and is measured in units of rads and rems or Systeme Internationale (SI) units of grays and sieverts).

Not only is the mechanism for pain relief unknown, but we also have no model to which to refer. Any direct attempt to determine what intramedullary and intraosseous biochemical changes occur with this radiotherapy which requires anatomic intervention perturbs the system. This is analogous to the Heisenberg uncertainty principle. Perhaps radiotracer research will provide some explanations.

The careful work of de Klerk et al. (4) in this issue is a Phase I dose escalation study to determine the safety (i.e., the maximum tolerated activity) of ^{186}Re-HEDP administered to patients with breast cancer metastatic to bone using activities from 1295 to 2960 MBq (35–80 mCi) in increments of 555 MBq (15 mCi). Unacceptable thrombocytopenia (Grade 3, platelets 25–50 × 10^9/liter and Grade 4, platelets <25 × 10^9/liter) occurred at the highest administered activity, and these workers placed the maximum tolerated administered ^{186}Re activity at 2405 MBq (65 mCi). A similar study by this group of ^{186}Re-HEDP for prostate cancer had previously determined that the

maximum tolerated dosage for treatment maximum of bone pain from this tumor was 2960 MBq (80 mCi) (5). The lower value for ^{186}Re activity in breast cancer is probably a reflection of marrow damage from chemotherapy. Thus, a lower activity of ^{186}Re in breast cancer yields similar marrow toxicity to a ^{186}Re dosage 23% higher in prostate cancer.

These workers also provide data that neither the normalized administered activity nor the bone scan index (BSI) adequately predict the percent of platelet decrement in breast cancer (4). This finding is in contrast to their data on ^{186}Re-HEDP in prostate cancer, where the percent of platelet decrease correlated with the BSI (p = 0.78, p < 0.001) (6). The level of administered activity also did not adequately predict this platelet decrement. They suggest that the bone scan does not reflect tumor burden in breast cancer to the same extent as the more osteoblastic (i.e., less osteolytic) prostate cancer bone metastases. It is likely that the affinity of reactive bone for the radiopharmaceutical, biological half-life, intramedullary tumor burden and distribution and varying degree of stem cell damage from previous therapy (less of a concern in prostate carcinoma, where chemotherapy is not commonly given), are more important variables in both myelotoxicity and pain response than administered activity, although toxicity becomes more likely as the dosage rises. Also, disseminated intravascular coagulation may be a cause of potentially lethal thrombocytopenia in cancer patients receiving these radiopharmaceuticals (7) and should be excluded before treating patients with bone pain from osseous metastases.

These considerations raise the issue of what the optimal radiopharmaceutical activity to be administered to reduce bone

pain with the least toxicity is. Should we give activities at maximally tolerated levels to our patients with bone pain from metastatic cancer where the painful site corresponds to increased uptake on bone scintigraphy? Is more better?

The current study of de Klerk et al. (4) and the similar study of dose escalation data in prostate cancer with ^{186}Re-HEDP (5) were both Phase I safety studies, and therefore no assessment of response, i.e., pain control, appears. These were not designed as efficacy (Phase II) studies. For both [^{32}P] orthophosphate and ^{89}Sr, however, there are data that show no increase in response with higher dosages. Some degree of pain control occurs in about 65%–80% of those treated (1,2,8,9).

Rhenium-186-HEDP, ^{153}Sm-EDTMP and ^{117m}Sn-DTPA have been administered to patients in activities varying by a factor of three or more for each radiopharmaceutical. The good pain responses, again in the 65%–80% range, for these newer radiopharmaceuticals, have not yet been reported to increase with higher activities. For ^{153}Sm, the dosage-response curve has been flat (10–12). Tin-117m and ^{186}Re dosage-response studies have not been published, but oral presentations have also suggested the lack of a dosage-response relationship. All of these radiopharmaceuticals will cause leukopenia and thrombocytopenia at some level of administered activity. These findings raise the question of what dosage of an individual radiopharmaceutical should be employed in comparative studies designed to determine which of these is most efficacious and least myelosuppressive. Should we then give the lowest dose showing a 65%–80% response?

An attempt to show that an 80% response is really different from a 65%

response, with an alpha (p) value of <0.05 and beta of 0.9, would require in excess of 700 patients for the study (13), a daunting and extremely expensive undertaking. An ongoing IAEA sponsored study comparing oral ^{32}P and intravenous ^{89}Sr now involves seven centers but will need similarly large numbers to show a real difference in efficacy. Note that in this study there are two variables, the radiopharmaceutical and the route of administration, because oral ^{32}P orthophosphate would be much less expensive if found to be as efficacious as [89]Sr.

In the Trans-Canada data (14) and another study from the U.K. (15) using dosages of 400 MBq (10.8 mCi) or 200 MBq (5.4 mCi) of ^{89}Sr, respectively, there was a delay in the appearance of new painful metastases when compared to a placebo. These activities exceed the 4 mCi or less activity usually administered in the U.S. If it could be shown that 5.8 mCi has this effect, which has not yet been reported with activities under 4 mCi, there would be a prompt increase in the activities of [89]Sr U.S. nuclear physicians prescribe. A Cincinnati study has documented a longer duration of response to ^{89}Sr with higher administered activities (7). Can these data be extrapolated to the other radiopharmaceuticals with shorter physical half-lives? We do not yet know.

The initial [186]Re-HEDP studies also used an administered activity of 35 mCi to deliver an estimated radiation dose to marrow of under 2 Gy and to tumor of 12–24 Gy based on a MIRD model (16). The response rate was 77%. Marrow and tumor dosimetry in the medullary space has been reexamined by this group and has proven to be far more complex than initially modelled (17). It is unlikely, based on numerous studies with all the radiopharmaceuticals listed above given at a wide range of dosages, that we can ever show statistically better response rates than about 80% from higher administered activities (1,2,8–12,16,18,19). Other variables, at least some of which have been noted above, are more important in obtaining a response.

It is heartening that deKlerk et al. (4) have documented that [186]Re-HEDP produces no significant marrow toxicity in activities up to 65 mCi (almost twice that used in the Cincinnati study) for breast cancer patients, who usually have had one or more regimens of myelosuppressive chemotherapy with some degree of resultant stem cell damage (16). In the Cincinnati group of 44 evaluable patients, seven women had breast cancer. Three of these seven patients, who had all received previous chemotherapy, re-

quired additional chemotherapy or teletherapy within 3–7 wk after receiving [186]Re-HEDP. All three experienced impressive resultant cytopenias and, clearly, one must be cautious in using chemotherapy or external beam radiation in such patients in this time interval after beta or electron-emitting radiopharmaceutical therapy when blood cell counts approaching platelet and leukocyte nadirs would be expected. Otherwise, the [186]Re related cytopenias in these patients were not clinically significant (16). This information should reassure medical oncologists and other referring physicians concerned about myelosuppression from radiopharmaceutical therapy for bone pain in breast cancer patients who have had prior chemotherapy. Chemotherapy should also not be given for four weeks prior to radiopharmaceutical treatment of bone pain.

We do not have data on the optimal administered activity of each radiopharmaceutical which will yield the least toxicity with highest therapeutic efficacy. If the currently available data survive further scrutiny, activities at the low end of the efficacious therapeutic range, yielding the least toxicity, would seem appropriate unless higher activities can be shown to prolong response (8). Lower activities are also more likely to permit repeated dosage of patients with recurrent pain. In addition, administered activities exceeding 30 mCi require hospital isolation in the U.S., so lower dosages mean shorter hospital stays.

A few comments on studying responses to these tracers are in order. Reproducible documentation of pain reduction is difficult, since the response we seek is a change in a subjective sensation—pain. Some older studies simply recorded that the patient stated he/she felt better. Semiquantitative activity scales, some more reproducible than others, have been employed (20,21). Quantitation of medication, sometimes requiring translation to morphine equivalents, has provided another objective measure of response. More pain could be experienced with activity, however, if the patient felt well enough at rest to try to be more active, or, there may be less pain with greater narcotic sedation, which could make the patient less capable of self care. Activity and pain scales must be interrelated.

Does evidence of a tumoricidal effect predict pain response, as it might if the pain were purely a mechanical phenomenon of tumor expanding in bone? In the Trans-Canada ^{89}Sr study, PSA levels fell and most patients had pain reduction (14). We do not know how strong the

correlation was. In the Utrecht study, CEA levels did not fall when elevated, even though the liklihood of some pain reduction in these [186]Re-HEDP treated patients should have approximated the 77% response rate of Maxon et al. (16). Here tumoricidal effects and pain reduction may not be tightly linked. After tumor is destroyed, osteoblastic activity is required to repair the bone containing necrotic tumor. Alkaline phosphatase levels fell in the Utrecht data with [186]Re-HEDP. Why would serum alkaline phosphatase levels fall during osteoblastic repair? Does this reflect a toxic effect on osteoblasts?

The flare phenomenon, a transient increase in bone pain, occurred in 50% of Utrecht patients, perhaps because higher activities were used in more of the patients than in the Cincinnati group, where flare reponse was described in 10% (16).

Many more questions remain to be answered in the use of these radiopharmaceuticals for the therapy of pain from osseous metastases:

1. What is the optimum administered activity for each of these radiopharmaceuticals, as indicated by efficacy, toxicity and duration of pain relief?
2. What is the "best" radiopharmaceutical when they are compared at these optimal doses?
3. Are divided or sequential dosages better than a single dosage?
4. Is there greater efficacy in combining a higher dose rate (shorter half life) radiopharmaceutical with one with a longer half life?
5. Can any of these radiopharmaceuticals be combined with chemotherapy for synergistic effects; e.g., with doxorubicin as a radiosensitizer?
6. Do any of these agents, alone or in combination, prolong life? Strontium-89 in the Trans-Canada study did not (14).
7. Should currently painless osteoblastic metastases be treated?
8. If a first dosage of radiopharmaceutical is ineffective, should a second be given?
9. Is individual lesion dosimetry necessary to predict response?

Dosage-response relationship studies in this important and expanding field of therapeutic nuclear medicine will be difficult to perform and expensive. We must move ahead quickly to optimize the care we bring to our suffering patients.

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Radioimmunoscintigraphy in Patients with Early Stage Cutaneous Malignant Melanoma

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CT and MRI examinations remain relatively insensitive for the detection of metastatic melanoma lesions, especially those of regional lymph nodes. Imaging cutaneous malignant melanoma patients with the Fab fragment of monoclonal antibody (MAb) NR-ML-05 labeled with ⁹⁹ᵐTc has been reported to increase the accuracy of staging. Our purpose in this study was to assess the sensitivity of ⁹⁹ᵐTc-labeled NR-ML-05 in detecting the spread of melanoma. **Methods:** Twenty-six adult cutaneous malignant melanoma patients were enrolled in this study and were followed for 6 to 60 mo after radioimmunoscintigraphy. At the time of imaging, 20 patients had their primary lesions resected, whereas the remaining 6 patients had their primary lesions intact. **Results:** Radioimmunoscintigraphy correctly detected 8 of 18 suspicious lesions as malignant, as well as 4 additional malignant lesions which had not been suspected previously. Radioimmunoscintigraphy also correctly identified 8 of the 18 suspicious lesions as benign. Two of the 18 suspicious lesions were found to be false negatives. The overall lesion sensitivity of radioimmunoscintigraphy was 86%. **Conclusion:** Twenty-four of the 26 patients were correctly staged by radioimmunoscintigraphy. The accuracy of staging of cutaneous malignant melanoma patients by clinical and or radiologic examinations (73%) was greatly improved with the use of radioimmunoscintigraphy (93%). These results suggest that radioimmunoscintigraphy may be a clinically useful adjunct to the current armamentarium for guidance of medical, and particularly surgical, therapy of cutaneous malignant melanoma patients.

Key Words: radioimmunoscintigraphy; monoclonal antibody; staging malignant melanoma

Cutaneous malignant melanoma presently has the most rapidly increasing cancer incidence in whites throughout the world. The age-adjusted incidence has quadrupled during the past 20 yr (*1*). The major cause of the present epidemic of malignant melanoma is thought to be increasing exposure of susceptible populations to ultraviolet radiation. The five-year survival rate, however, has increased 33% over the past 25 yr, and this improvement is thought to be attributable to earlier diagnosis and better recognition of cutaneous malignant melanoma rather than from refinements in treatment (*2,3*).

Most primary physicians are now sensitive to the danger presented by pigmented cutaneous lesions that grow and develop satellite lesions over a short period of time. When a suspicious pigmented lesion is removed and a histologic diagnosis of malignant melanoma is confirmed, immediate wide surgical excision is the initial treatment of choice.

The American Joint Committee on Cancer utilizes the TNM (T = tumor, N = nodes, M = metastases) system for staging cutaneous malignant melanoma. In this internationally accepted system, the status of the regional lymph nodes is a critical component of the staging of melanoma. Most patients in the U.S. currently are diagnosed as having Clark's histologic level three (III) with no clinical evidence of metastases (Stage I).