INVITED COMMENTARY

Radionuclides for Metastatic Bone Pain Palliation: A Need for Rational Re-Evaluation in the New Millennium

Pain is both a blessing and curse for humanity. The onset of pain serves as a benefactor when it convinces the patient to seek medical aid early, at a time when the pathophysiologic process is still reversible. However, the same benefactor becomes a curse in the terminal stages of patients' lives, especially for those with metastatic bone cancer.

PAIN TRANSMISSION

Recent studies have greatly advanced our understanding of the origin and transmission of pain, which involves central and peripheral control mechanisms activated by the release of various chemicals (*1*). The primary afferent pain neuron, located in the dorsal root ganglia, sends out peripheral and central fibers. The peripheral fiber travels to distant organs in the body to make connections with cells in the bone, muscle, skin, subcutaneous tissue, etc. At its terminal end, the peripheral fiber has receptors for pain (Fig. 1). The central fiber travels towards the spinal cord and synapses with the secondary neurons in the dorsal horn. Fibers from the secondary neurons cross the midline to the opposite side and travel centrally to synapse with the tertiary neuron in the thalamus. From there the terminal fibers reach cells in the cerebral cortex. There are different types of pain with different types of pain fibers for transmission. Metastatic bone pain is a nociceptive somatic pain, initiated and maintained through local tissue injury.

Much of our current knowledge about pain control has emerged from studies using opioids in animals and humans. Opioids exert their antinociceptive effect by acting on the μ, δ, and κ receptors of neurons throughout the nervous system. This widespread neuronal action is responsible for their central sedative effect. They alter the threshold, perception, and response to pain. Opioid receptors from the dorsal root ganglia are transported both peripherally to the nerve terminal on the tissue cells and centrally toward the spinal cord (*2*). At the site of malignant invasion, tumor cells, platelets, white blood cells, immune cells, and other inflammatory cells accumulate and release the chemicals that are responsible for the onset and continuation of pain (Fig. 1).

Nonsteroidal anti-inflammatory drugs and opioids have been the mainstays for relief of metastatic bone pain. Despite the availability a variety of other agents, patients often suffer from pain because of substandard and inadequate care (*3*). Although opioids have been available for more than 100 y, it is only recently that the medical community, public, and patients have accepted the role of these medications in the control of metastatic bone pain. Irrational and inappropriate concern for respiratory depression and drug addiction were primarily responsible for such a long delay in acceptance (*4*). Improper pain assessment, a high priority for cancer control, a low priority for symptom control, and underdosing, all contributed towards poor management of cancer pain (*5*).

THE PAIN CYCLE

Stress is a potent stimulus for nociceptive pain. The impression that a pain may be uncontrollable produces stress for patients, which leads to increased suffering and despair, and decreases the patient's performance (*6*). An effective pain management strategy requires breaking off this cycle using all available means. Many patients and members of the general public have changed their priorities to place more importance on quality of life than on length of survival in the terminal stages of disease, compelling health care professionals to re-evaluate old ideas about opioids. Health care professionals now accept individual, patient-controlled opioid analgesia as both feasible and effective (*7*).

An effective pain control strategy, however, requires patients to take large quantities of opioids, often as much as 60–200 mg/day. This large dose causes severe side effects, including nausea, vomiting, constipation, and central sedation, all of which combine to decrease quality of life. Patients must take large doses of antiemetics and laxatives to counteract nausea and constipation, respectively. Central sedation increases drowsiness, resulting in frequent falls, bone fractures, and driving accidents. Supplemental therapy with local radiation, wide-field radiation, biphosphonates, or radionuclides can significantly decrease the dose of opioids for most patients or completely eliminate the need for the medications in a few patients (*8,9*).

MERITS OF RADIONUCLIDES

^{32}P, ^{89}Sr, and ^{153}Sm are 3 of the radionuclides approved by the U.S.

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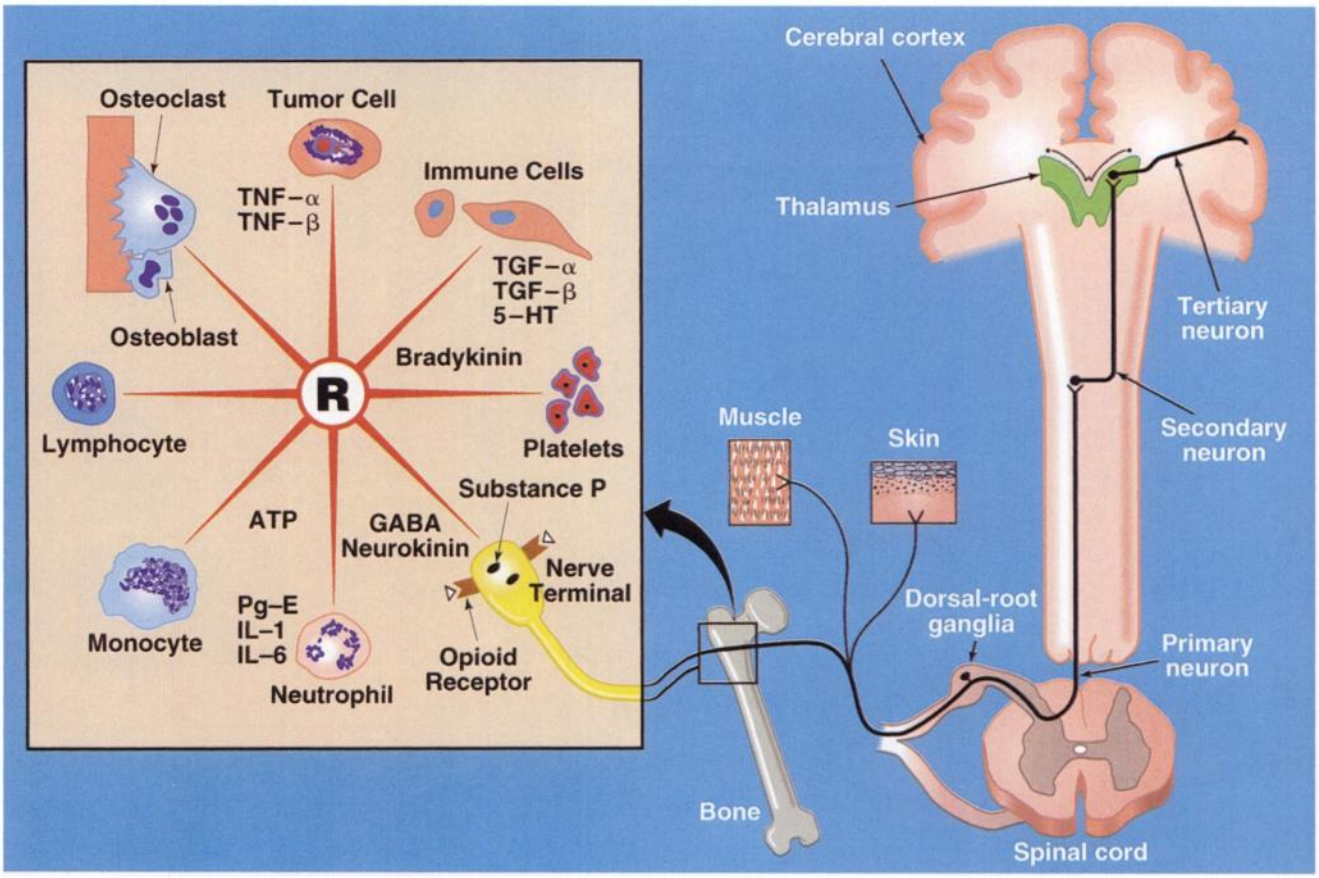

FIGURE 1. Origin, transmission, and control of metastatic bone pain. Pain originating at primary afferent nerve terminal on tissue cells is carried to cerebral cortex by secondary and tertiary neurons located in spinal cord and thalamus, respectively. Varieties of chemicals released by different cells near nerve terminal at metastatic site initiate and modulate pain threshold and its perception. Radionuclides (R) relieve pain by delivering radiation to inflammatory, immune, and tumor cells, which release chemicals that lower pain threshold or promote pain transmission. GABA = γ amino butaric acid; Pg-E = prostaglandin E; IL = interleukin; TGF = transforming growth factor; TNF = tumor necrosis factor; HT = hydroxytryptamine.

Food and Drug Administration for palliation of metastatic bone pain (*10–15*). Despite the use of ^{32}P in large numbers of patients over many years (Table 1), there is a great reluctance to use this radionuclide. This is mainly because of perceived notions about toxicity—a situation quite similar to the opioid fears already cited (*10*). ^{89}Sr or ^{153}Sm are quite expensive and have not yet gained much popularity. Unlike opioids, which affect the entire nervous system, radionuclides exert their action mainly on cells at the peripheral nerve endings, where inflammatory, immune, and malignant cells accumulate and release chemicals that modulate pain at the site of malignant invasion (Fig. 1). Radionuclides do not cause any central sedation. Local or wide-field external radiation is much more expensive than ^{89}Sr or ^{153}Sm and appears inappropriate when there are multiple sites of metastatic foci.

RECENT DATA

Should the perceived toxicity of ^{32}P be a major concern for health care professionals in the management of metastatic bone pain in the new millennium? Two recent publications in the *Journal of Nuclear Medicine* provide some solid data to answer this question. A study by Nair (*16*), completed

TABLE 1
Comparison of Benefits and Costs of 3 Approved Radiopharmaceuticals for Metastatic Bone Pain Palliation

Agent	Half-life (d)	Unit dose in MBq (range)	No. of patients treated	Response mean	Pain relief (wk)	Cost of unit dose
^{32}P-phosphate	14.26	370 (296–555)	871*	74%†	10	$390
^{89}Sr-chloride	50.53	148 (111–370)	318‡	80%§	10	$2900
^{153}Sm-EDTMP	1.95	2590 (1850–5180)	243‖	77%#	10	$2850

*Patients from studies reported in (*10*) and (*16*).
†From data reported in (*16*).
‡Patients from studies reported in (*9*) and (*16*).
§From data reported in (*16*).
‖Patients from studies reported in (*11–15*).
#From data reported in (*13*) and (*15*).
EDTMP = ethylene diamine tetramethylene phosphonate.

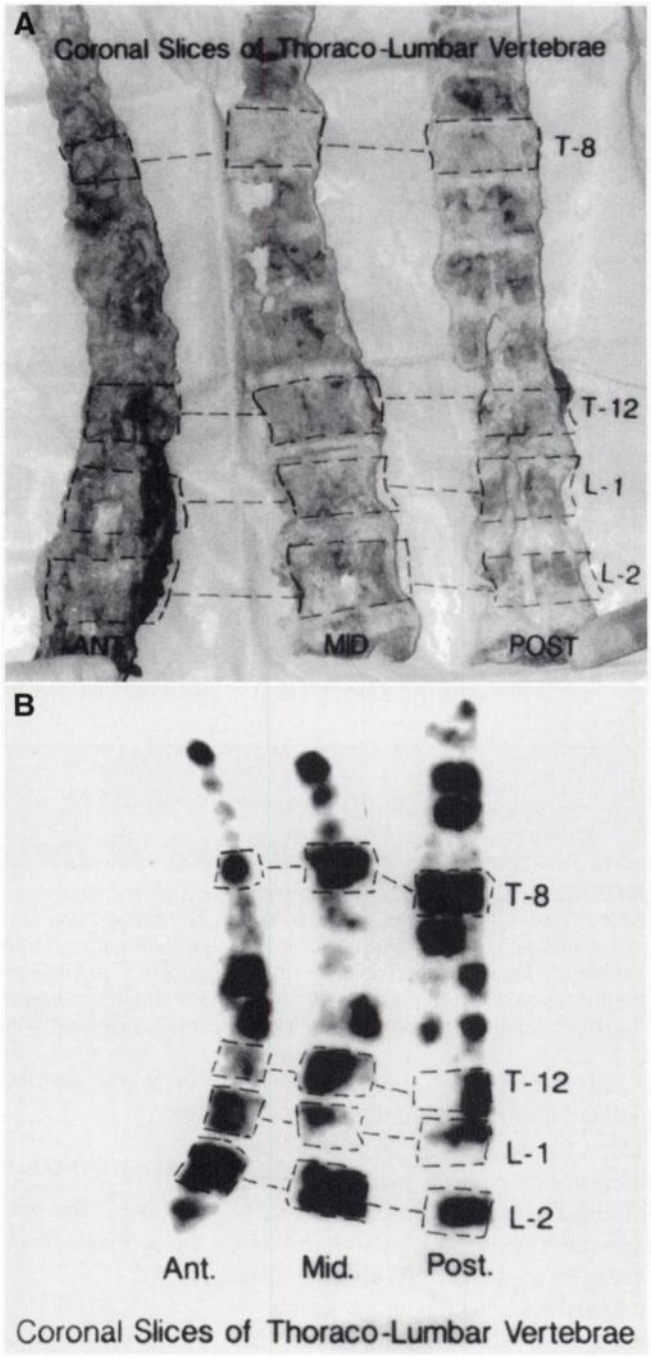

FIGURE 2. Localization of ^{117m}Sn-diethylenetriamine pentaacetic acid (DTPA) in bone. (A) Photograph shows 3 coronal slices, each 5 mm thick, of thoracolumbar vertebrae of a patient who died 47 d after receiving 18.6 mCi dose of ^{117m}Sn-DTPA for metastatic bone pain palliation. (B) γ camera image of slices shows homogenous (T8, L2) and heterogenous (T12, L1) ^{117m}Sn distribution, indicating normal bone marrow in midst of metastatic foci. Low-energy electrons have potential to spare nearby normal bone marrow and deliver maximum radiation to tumor site. (Reprinted with permission of [*18*]).

under an International Atomic Energy Agency (IAEA)-approved protocol and using the most modern method of data collection and analysis, showed that both 444 MBq (12.0 mCi) ^{32}P administered orally and 148 MBq (4 mCi) ^{89}Sr administered intravenously are safe, effective, and relieve pain. The time to onset of pain, the time to maximum pain relief, and the degree and duration of pain relief were similar for both agents. More patients treated with ^{32}P returned to normal mobility than those treated with ^{89}Sr. Cell counts decreased transiently with both agents and slightly more severely with ^{32}P, but no patients required therapy for decreases in cell count, and counts returned to normal levels within a year (*16*).

In the current issue of the *Journal*, Bouchet et al. (*17*) outline the variable to be considered when selecting a radiopharmaceutical for the palliation of metastatic bone pain. Applying the most modern dosimetry methods, they calculated the relative advantage factor (RAF) for each of 8 current and potential pain palliation radionuclides (^{32}P, ^{33}P, ^{89}Sr, ^{186}Re, ^{153}Sm, ^{177}Lu, ^{169}Er, and ^{117m}Sn). After a detailed analysis and discussion they concluded that radionuclides with low-energy electrons (^{117m}Sn and ^{33}P) with a tissue range of 0.05–0.15 mm are the agents of first choice for the palliation of metastatic bone pain. This recommendation appears logical,

considering the fact that there is a substantial amount of normal bone marrow in the midst of most bone malignancies (*18*). If the therapy goal includes both pain palliation and disease control, then protection of the marrow is very important (Fig. 2).

RE-EVALUATION

We suggest that the goals and objectives of radionuclides for metastatic bone pain in the new millennium should be separated into 2 major categories: pain palliation and pain palliation plus disease control. Recent literature provides valid data (Table 1) to support this new classification. ^{32}P would be the clear winner for pain palliation because of its low cost, about 10% of the cost of the other 2 approved agents. Patients, family members, primary care physicians, health maintenance organizations, and insurance agencies should view $390.00 per unit dose as quite reasonable for 10 wk of comfort in terminal pain management. It is has been difficult to convince patients or health care management to accept ^{89}Sr or ^{153}Sm at a cost of nearly $3000 for 2–3 mo of comfort (Table 1). Because of the heavy financial burden, many patients choose to suffer instead of opting for this expensive treatment.

Under this new classification, ^{89}Sr and ^{153}Sm and other beneficial radionuclides would be reserved for patients for whom the clinical goal is both pain palliation and disease control. Newer agents, such as ^{169}Er, ^{117m}Sn, and ^{33}P, would become more attractive under this classification, leading to their rapid development and approval (*17*). These agents, which appear to have low bone marrow toxicity, may enable treatment of patients as soon as multiple bone metastases occur, long before the onset of pain. The higher costs then would be justifiable, because palliation would be linked to disease control, prolonging the quality of life and delaying or completely stopping the progression of malignancy.

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