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REVIEW ARTICLE

The use of radioisotopes for palliation of metastatic bone pain

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Summary

Bone pain associated with advanced prostate and other cancers is a frequent and significant complication. Pharmaceutical therapy of bone pain includes nonsteroidal analgesics and opiates. While external beam radiation therapy remains the mainstay of pain palliation of solitary lesions, bone-seeking radiopharmaceuticals have entered the armamentarium for the treatment of multiple osseous metastases. The 3 radioisotopes currently approved for treatment of pain (strontium-89/^{89}Sr, samarium-153/^{153}Sm and rhenium-186/^{186}Re) are discussed in this review including the approved dose, method of administration and indications for use.

Key words: bone pain, osseous metastases, radiopharmaceutical therapy

Introduction

Bone metastases are a frequent complication of cancer occurring in up to 70% of patients suffering from advanced breast or prostate cancer and in up to 30% of those with cancers of the lung, bladder and thyroid [1]. Metastatic bone disease contributes significantly to the morbidity and mortality of patients with advanced cancers.

The major complications associated with bone involvement are severe pain, spinal cord compression and pathological fracture, all of which restrict mobility and sleep, reducing or even ruining the patient's quality of life.

The pathophysiology of bone metastasis and related complications is complex. The exact mechanism of cancer pain is unknown and is postulated that the pain may be due to the presence of tumor in the bone. Normal bone undergoes continuous remodeling that is essential to maintain its mechanical function. The process is performed by a multicellular unit formed by two different cell types, osteoclasts and osteoblasts. Osteoclasts reabsorb bone whereas osteoblasts replace bone [2].

During bone resorption growth factors and mineral ions are released from the bone matrix [3]. When bone metastases occur a cycle of signaling takes place that results in increased osteolytic activity. Tumor-derived factors stimulate osteoclast – mediated bone resorption, whereas the growth factors released from the bone matrix stimulate the tumor cells to grow and secrete additional cytokines. This leads to osteopenia and increased risk of developing fractures and, when lesions are in the vertebrae, spinal cord compression (Figure 1).

The primary malignant neoplasm promotes new blood vessel formation and these vessels carry cancer cells to capillary beds in the bone. Aggregates of tumor cells and other blood cells form embolisms that lodge in distant capillaries in the bone. Cancer cells can adhere to vascular epithelial cells to escape the blood vessels. As cancer cells enter the bone, they contact factors in the bone microenvironment that support the growth of metastases (Figure 2) [4,5]. As shown in Fig-

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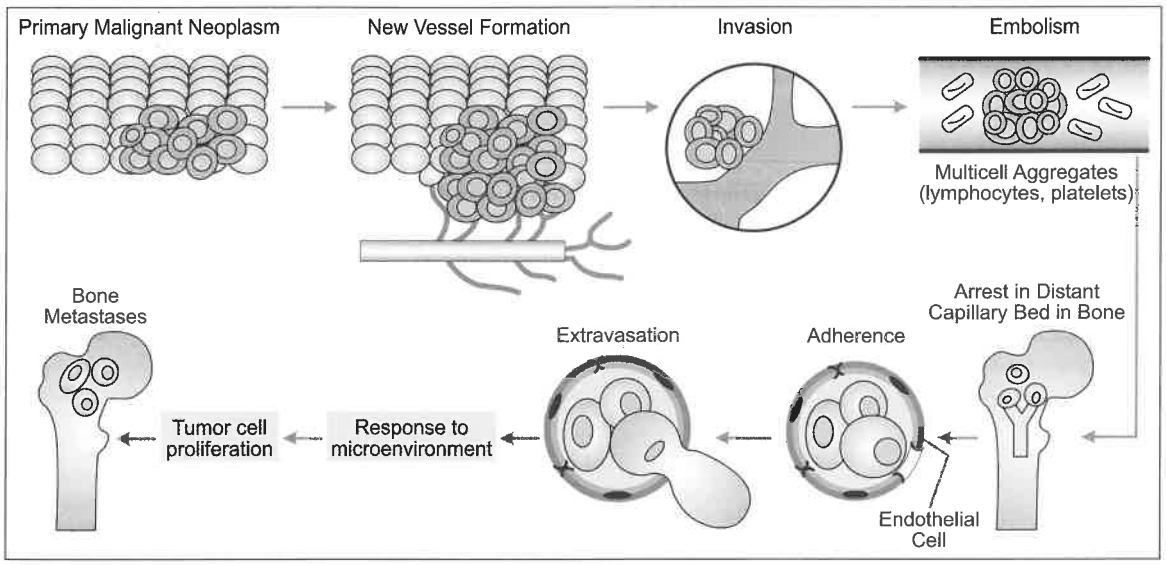
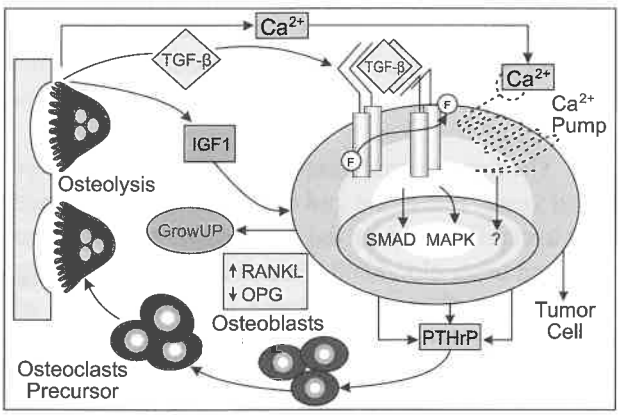


Figure 1. Development of bone metastasis. The primary malignant neoplasm promotes new blood vessel formation, and these blood vessels carry cancer cells to capillary beds in the bone. Cancer cells can adhere to vascular epithelial cells to escape the blood vessels. As cancer cells enter the bone, they contact factors in the microenvironment of the bone that support the growth of metastases (From Mundy [5]).

ure 2 interactions between tumor cells and osteoclasts cause osteoclast activation and bone destruction and can stimulate aggressive growth and behavior of tumor cells. Tumor cells produce PTHrP (parathyroid hormone-related peptide), which activates osteoblasts to produce RANKL (receptor activator of nuclear factor-kb ligand) and downregulate OPG (osteoprotegerin). Osteoclast precursors are activated which leads to osteolysis. Bone-derived growth factors including TGF-b (transforming growth factor-b) and IGF-1 (insulin-like growth factor-1) are then released and extracellular calcium concentrations are raised. When growth factors bind to receptors on the tumor cell surface autophosphorylation (P) and signaling through SMAD (cytoplasmic mediators of most TGF-b signals) and MAPK (mitogen-activated protein kinase) occur. Extracellular calcium binds and activates a calcium pump. Signaling through these pathways results in proliferation of tumor cells and production of PTHrP.



For abbreviations see text

Figure 2. Osteolytic bone metastasis. Interactions between tumor cells and osteoclasts cause osteoclast activation and bone destruction and can stimulate aggressive growth and behavior of tumor cells. Tumor cells produce PTHrP, which activates osteoblasts to make RANKL and downregulate OPG. Osteoclast precursors are activated, which leads to osteolysis (From Mundy [5]).

Skeletal metastasis is a multifactorial process in which several biologic processes play a role leading to interaction between host and tumor cells. Cellular invasion and migration, cell matrix adhesion or cell-to-cell adhesions, interaction with endothelial cells, regulation of growth factors, and stimulation of osteoclasts and osteoblasts are thought to the contribute to development of skeletal metastasis. Cadherins, integrins, immunoglobulins, selectins and CD44 are some of the molecules implicated in loss of cellular adhesion that causes cell matrix detachment, invasion and migration [5-8].

Invasiveness is mediated by several enzyme systems, including serine proteases, of which matrix metalloproteins and urokinase plasminogen activation system are thought to be most important. Cellular motility is critical for tumor cells to develop distant metastasis. Motility is mediated by several factors in-

cluding growth factors (TGF-b, bone morphogenic proteins -BMPs- and epidermal growth factor - EGF), hyaluronians, components of matrix, and host-or-tumor secreted factors [9,10].

Bone metastases often present with severe bone pain, especially in advanced disease stage. Bone pain is thought to be distinct from neuropathic or inflammatory pain, where there is upregulation of the glial fibrillary acidic protein in the spinal cord, indicating astrogliosis [11]. The major mechanism of pain from small metastases appears to be the stimulation of nerve endings in the endosteum by a variety of chemical mediators. Receptors for many of these mediators are expressed by primary afferent neurons. Peripheral sensitization leads to increased release of substance P from nociceptors, even with minor stimulation. Sensitization also occurs centrally in the dorsal horn of the spinal cord, which leads to allodynia and hyperalgesia. The spinal cord may show marked astrocytosis, increased expression of c-Fos (a general marker of neuronal activity), and a peptide-dynorphin [12]. Larger bone metastases produce stretching of the periosteum which leads to pain [13]. As a result of local bone destruction, there may be activation of pain receptors in local nerves. Macrofractures and microfractures might also be one of the contributing causes of bone pain (Figure 3) [14].

Management of bone pain includes analgesia, antitumor agents, radiation, radiofrequency ablation (RF), hormones, bisphosphonates, chemotherapy and surgery. Localized sites of involvement can be treated with surgery, RF ablation or external beam radiation, whereas radiopharmaceuticals, hormones and chemotherapy are used to treat more diffuse bone involvement. In general, a combination of systemic and local modalities is required and no single treatment regimen is efficacious for an extended period of time.

For many patients with multiple symptomatic osteoblastic bone metastases who have relapsed following an initial course of hormonotherapy or chemotherapy, bone-targeted systemic radionuclides have emerged as a valuable treatment option [15]. Four radionuclides are currently approved for the treatment of bone pain: first generation phosphorus-32 (^{32}P), second generation ^{89}Sr, and third generation ^{186}Re and ^{153}Sm.

Although ^{32}P was initially used to treat bone metastases originating from breast and prostate cancer, considerable myelosuppression reduced its usefulness. Therefore, this review focuses on ^{89}Sr, ^{153}Sm and ^{186}Re.

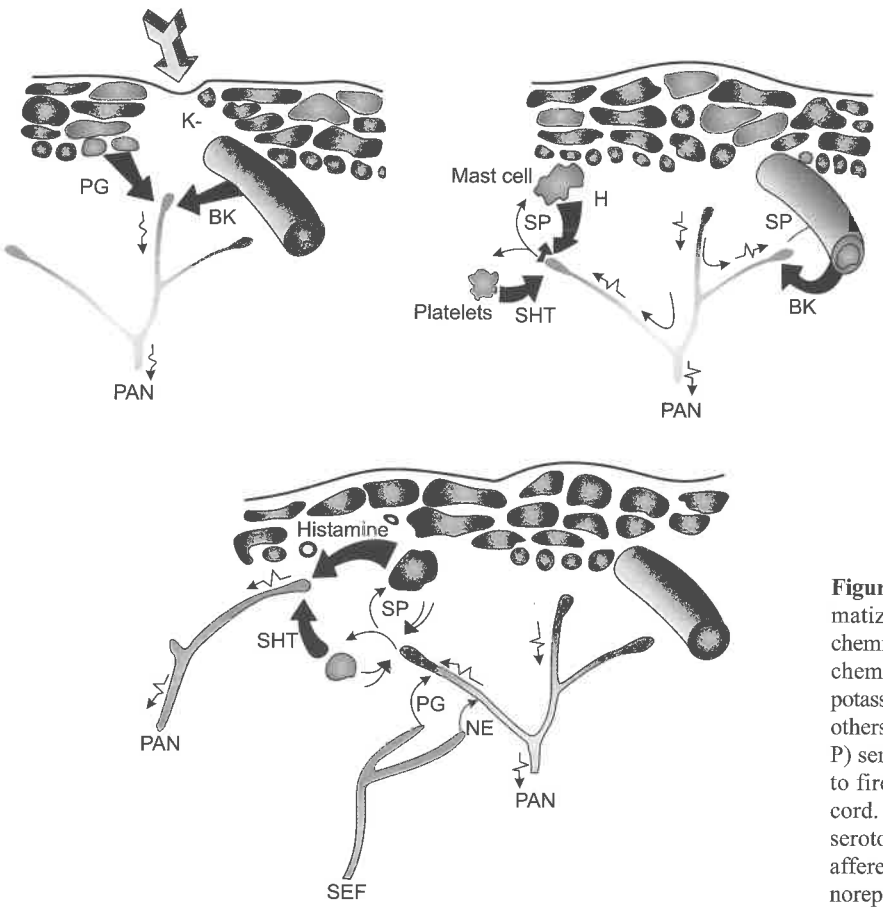


Figure 3. Pain mechanism. When tissue is traumatized and cells are damaged, a number of chemicals are released near the pain fiber. Some chemicals (bradykinin, serotonin, histamine, potassium ions, norepinephrine) stimulate while others (leukotrienes, prostaglandins, substance P) sensitize the pain fiber to be excitable and to fire an action potential toward the spinal cord. BK: bradykinin, SP: substance P, SHT: serotonin, PG: prostaglandins, PAN: primary afferent nonciceptor, K: potassium ions, NE: norepinephrine (From Abelóff [15]).

These isotopes are given systematically and are localized in sites of active bone turnover, which ensures that all metastases are treated simultaneously. Decay properties, such as half-life and particle energy, play significant roles in clinical characteristics of these agents, such as onset and duration of palliative effects and degree of time to recovery from myelosuppression.

All these isotopes emit β-particles (electrons) with sufficiently long half-lives to provide cytotoxic irradiation to the adjacent malignant cells. In addition, ^{153}Sm and ^{186}Re also emit γ photons, which has the advantage of allowing external imaging of isotope distribution. Once eligibility is established, the patient is treated in outpatient setting and is instructed about the radiation safety precautions (Table 1).

Radioisotopes are generally given on an outpatient basis but in some countries regulations require patients to be admitted to hospital after being given γ-emitting radioisotopes. Radioisotopes are given intravenously and should only be given by a clinician trained in the use of unsealed radioactive sources for treatment. Secure intravenous access, preferably with a flexible indwelling catheter, is essential to avoid extravasation and the consequences of local tissue damage. γ rays can pass out of the patient's body, presenting an external risk to bystanders. The β-particles emitted by radioisotopes bring about the destruction of malignant cells, but they have a short range and, therefore, pose little threat to clinicians, nurses, or family members. Radioisotopes are mainly excreted in urine, so precautions must be taken with urine or blood spills. Patients, their relatives and hospital staff need to be informed of the need for care in this respect, for instance the proper use of toilets. Incontinent patients should be catheterised if they are to receive radioisotope treatment. These precautions are necessary only for the first 10 days after treatment when activity in the blood and urine is greatest. Concerns about exposure of mortuary or crematorium staff to radioactivity are unfounded. Schramel investigated the possible radiation exposure of pathologists who undertook an autopsy of a patient who died 4 days after receiving 162 MBq of ^{89}Sr. The dosimeters worn by the pathology staff read zero at the end of the procedure [16]. The UK National Radiological Protection Board have made calculations based upon the most pessimistic assumptions, and the widest probable use. These calculations show that the resulting radiation dose to the population would be insignificant compared with the average natural background levels [17].

Table 2 shows the characteristics and pretreatment criteria to be used for selection of patients for every isotope.

Table 1. Safety precautions to be taken by patients receiving radiotherapy and their care givers

Hospital staff
Wear protective shoe covers, gloves and apron
Work quickly but efficiently to reduce exposure
Maintain the greatest distance possible consistent with the care of the patient
Observe rules for handling of blood and urine
Wash hands after leaving the patient
Patient
Use a flushable toilet rather than a urinal
Flush toilet twice to reduce environmental contamination
Wipe any spilled urine with a tissue and flush away
Wash soiled clothes or linen immediately and separately
Wash away spilled blood from cuts

^{89}Strontium

^{89}Sr, an element that behaves biologically like calcium, was first discovered in 1790 by Adair Crawford in mineral mines near the small village of Strontian, Argyll, U.K. Strontium has the atomic number 38 and is immediately below calcium in the periodic Table of elements. Not surprisingly, therefore, ^{89}Sr follows the same metabolic pathway *in vivo* as calcium and is readily incorporated into the inorganic matrix of bone [18]. ^{89}Sr is cleared rapidly from the blood with at least 50% of the dose localized in the skeleton, the uptake being 10 times greater for metastatic tumor lesions than for healthy bone [18]. The usual therapeutic dose is 148 MBq (4 mCi).

Table 2. Comparison of the properties of some radioisotopes

Radioisotope	*Carrier ligand*	*Half-life (days)*	*β energy (MeV)*	*γ energy (MeV)*	*Maximum range (mm)*
^{89}Strontium	Chloride	50.5	1.46	_	2-3.0
^{153}Samarium	EDTMP	1.9	0.81	0.103	2.5
^{186}Rhenium	HEDP	3.7	1.07	0.137	4.5

EDTMP: ethylenediaminetetramethylene phosphonic acid, HEDP: 1-1 hydroethylidene diphosphate

After intravenous administration ^{89}Sr is localized in the bones according to the osteoblastic activity. Of the ^{89}Sr that is not concentrated in the bones, about 80% is excreted through the kidneys and about 20% through the gastrointestinal system [19,20]. Although its biologic half-life is 4-5 days, about 20% is retained in the body even after 90 days [20]. ^{89}Sr therapy can relieve bone pain for up to 14 months and is recommended for use in patients with moderate pain and reasonable life expectancy [21]. Response rates range from 60 to 84% [22]. The onset of pain relief is generally within 7-21 days, with mean duration of relief of about 6 months [23,24]. Transient increase of bone pain (painful flare) may occur in the first 2-3 days after treatment. This is usually mild, self-limited and controlled with analgesics. A flare usually heralds a good treatment response. Patients can be treated after 90 days though multiple therapies may lead to greater marrow toxicity [25].

The toxic effects associated with ^{89}Sr seem to be mild and reversible. About 15% of patients have increased pain (flare or after 1-5 days, which can last 4 days). Haematological toxic effects are the most commonly observed side-effects, with a reduction in white cell count of 12-65% occurring in 15-80% of the patients. Platelet counts fall by an average of 29% in 30-80% of the patients, whereas red cell counts change negligibly or not at all. Generally, blood counts return to normal values and no intervention is needed [24].

Several studies have demonstrated no significant differences between response to ^{89}Sr and response to hemibody irradiation [26,27]. Concurrently administered chemotherapy is effective in enhancing pain relief and delaying the appearance of new painful metastases, however, combining ^{89}Sr with chemotherapy does not increase the overall pain relief response rates [28]. Although the agent is useful for bony pain palliation, there is no survival benefit, even when a dose of 399.6 MBq is used [29,30]. In patients with androgen-independent prostate cancer and severe bone pain, combined treatment with ^{89}Sr and doxorubicin resulted in a mean survival of 28 months compared with 17 months for patients treated with doxorubicin alone [31]. The use of ^{89}Sr can help reduce the lifetime health-care costs by decreasing both the need for radiotherapy and the need for narcotics and hospitalization.

^{153}Samarium

^{153}Sm is a lanthanide with atomic number 62 and amolecular mass of 150.36.^{153}Sm is prepared by neutron irradiation of enriched $^{152}Sm_2O_3$. Under acid conditions induced by hydrochloric acid, $^{153}SmCl$ is produced, which can then be complexed with the calcium salt of ethylenediaminetetramethylene phosphonic acid (EDTMP) to give ^{153}Sm-EDTMP.

In the late 1990s, ^{153}Sm was approved in the USA, Australia, Canada and Europe for the treatment of pain from cancer that had spread to the skeleton. It has a physical half-life of 1.9 days and decays by β emission. The β particle has a maximum energy of 0.81 MeV, a mean energy of 0.23 MeV, and an average soft-tissue range of 0.6 mm.

^{153}Sm- EDTMP complex localizes in the skeleton according to the osteoblastic activity. After intravenous injection < 1% remains in the blood at 5 h. About 65% of the dose remains in the skeleton [32]. The urinary excretion is nearly complete by 6 h [33]. The therapeutic dose of ^{153}Sm is 37 MBq/kg (1mCi/kg) [28]. The major toxic effect observed was myelosuppression, with thrombocytopenia being dose limiting in 20-43% of patients. Platelet nadir occurred between days 16 and 45 (median 28 days), but thrombocytopenia was reversible in up to 97% of the patients [34]. Pain palliation occurs in 62-74% of the patients with better overall responses at higher doses. A transient rise in bone pain (flare) was seen in 70-95% of the patients [35,36]. Patients with extensive osseous metastases were more likely to have myelotoxicity, probably due to a fragile marrow [37].

^{153}Sm is the most widely used pain palliation radiopharmaceutical agent in the USA. Its ease of use, the ability to image its distribution, and its clinical results make it attractive, while issues with availability, radiation safety and potential irreversible myelosuppression limit wider use.

^{186}Rhenium

^{186}Re is complexed with 1-1 hydroethylidene diphosphate (^{186}Re-HEDP), which bonds to hydroxyapatite crystals by forming hydroxide bridges in a hydrolysis reaction. This process is thought to be mediated by the metabolic activity of osteoclastic cells, and the concentration in bones allows high dose of ^{186}Re-HEDP to irradiate malignant cells in the bones. ^{186}Re-HEDP binds to plasma proteins in a time-dependent interaction, and is cleared from the plasma with a half-life of 3.7 days and emits a β-particle with a maximum energy of 1.07 MeV and an average soft-tissue range of 1.1 mm [38]. About 70% of the activity is excreted in the urine within 24 h, and the maximum tolerated activity is 2960 MBq for patients with metastatic prostate cancer and 2405 MBq for patients with breast cancer. At therapeutic doses the bone marrow-absorbed dose is

about 1.04 mGy/MBq. Pain relief is established early and the tumor-to-bone marrow absorbed dose ratio is 14: 1, suggesting its clinical relevance in patients with more compromised bone marrow reserve [39]. Typical marrow recovery times range from 4 to 6 weeks. Other reported side effects are mild pain (flare phenomenon - 6.5%), occurring in the first week and lasting 2-4 days [40]. Its role in androgen-independent prostate cancer and many other cancers has also been studied, with reported response rates of about 50-98% [41,42].

Conclusion

Painful bone metastases are a common and significant problem for patients with advanced prostate or breast cancer. There has been increased clinical interest in the palliative use of radionuclides to treat metastatic bone cancer, and the data now available provide strong evidence that they are effective in relieving pain in substantial numbers of patients.

One of the major drawbacks in the investigation of the efficacy of radioisotopes in patients with bone metastases is the assessment of bone pain. Pain intensity is a subjective assessment and is not readily quantifiable with reproducibility between patients and studies. Pain relief and decrease in analgesic consumption can be expected in the majority of the patients treated. The variability in assessment of pain response reported in the published works indicates the need to develop validated instruments to quantify pain response accurately and consistently.

Some other issues need clarification, such as which isotope and what schedule to use. All seem to be effective in reducing bone pain, and have similar toxic effect profiles. However, comprehensive and up to date cost analyses will be needed. When radioisotopic treatment should be started and which categories of patients will probably respond are also not clear. These questions need further investigation if the full clinical benefit of radioisotopes is to be established.

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