Painful Boney Metastases

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Up to 90% of patients with metastatic or advanced stage cancer will experience significant cancer-related pain. Approximately half or more of patients diagnosed with cancer may experience bone pain. It has been estimated that tumor metastases to the skeleton affects roughly 400,000 US citizens annually. Carcinoma from breast, lung, and prostate cancers account for approximately 80% of secondary metastatic bone disease. Bone metastases may cause devastating clinical complications associated with dramatic reductions in quality of life, mobility, and independence, as well as excruciating refractory pain. Associated complications from osseous metastases also present a substantial economic burden. Currently, there are still a significantly high number of patients suffering with unrelieved pain from osseous metastases. Treatments for painful osseous metastases may not only diminish pain but also may improve quality of life and independence/mobility, and reduce skeletal morbidity, potential pathologic fractures, spinal cord compression, and other “skeletal-related events.” Treatment strategies for painful osseous metastases include the following: systemic analgesics, intrathecal analgesics, glucocorticoids, radiation (external beam radiation, radiopharmaceuticals), ablative techniques (radiofrequency ablation and cryoablation), bisphosphonates, chemo-therapeutic agents, inhibitors of RANKL–RANK interaction (eg, denosumab), hormonal therapies, interventional techniques (eg, kyphoplasty), and surgical approaches. Although the mechanisms underlying the development of bone metastases remain incompletely understood, there appears to be important bi-directional interactions between the tumor and the bone microenvironment. A greater understanding of the pathophysiology of painful osseous metastases may lead to better and more selective targeted analgesic therapy. Additionally, potential future therapeutic approaches to painful osseous metastases may revolutionize approaches to analgesia for this condition, leading to optimal outcomes with maximal pain relief and minimal adverse effects.

Keywords: pain, osseous, bone, cancer, metastases, denosumab, radiation, radiopharmaceuticals

INTRODUCTION

World health experts estimated that in 2008 there were more than 12 million new cases of cancer diagnosed and 7.6 million deaths from cancer.1 It has been reported that up to 75%–90% of patients with metastatic or advanced stage cancer will experience significant cancer-induced pain.2–5 Approximately half or more of patients diagnosed with cancer may experience bone pain.6 Breast, lung, and prostate cancers are collectively responsible for approximately 80% of secondary metastatic bone disease.7 Other common types of cancer, such as thyroid, lung, and kidney carcinomas, also display significant osteotropism. In general, when a tumor grows in the bone it may become more of a challenge to achieve a “cure” status, and it may cause devastating clinical complications, such as intractable severe pain, pathological fractures, spinal cord and nerve compression, hypercalcemia, and bone marrow aplasia, collectively referred as “skeletal-related events” (SREs).7 Not all

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patients with bone metastases have pain, but approximately 83% of patients with osseous metastases complain of pain at some point with wide variation in pattern and severity.\textsuperscript{10-12} Payne and Janjan\textsuperscript{10} recommend specialized interdisciplinary cancer center bone metastasis clinics for patients with painful osseous metastases, if available. They have published an algorithm for assessment and management of these patients.\textsuperscript{11} Treatment strategies have used various therapies for the treatment of painful osseous metastases including bisphosphonates,\textsuperscript{12} chemotherapeutic agents—mitoxantrone (a chemotherapeutic agent that inhibits DNA synthesis),\textsuperscript{13} hormonal therapy, and interventional and surgical approaches.\textsuperscript{14} Additional agents may include systemic analgesics, steroids, radiation (external beam radiation, radiopharmaceuticals), and ablation [radiofrequency ablation (RFA) and cryoablation], and intrathecal analgesics.

Metastatic bone disease is classified as osteolytic and osteoblastic; however, usually lesions lie within a spectrum of these 2 entities (Figure 1). As denoted by their names, osteolytic metastases, which are considerably more common, are characterized by significant bone disruption because of the augmented osteoclastic activity; on the contrary, osteoblastic metastases are characterized by overproduction of osseous tissue by activated osteoblasts.\textsuperscript{15}

PATHOPHYSIOLOGY OF BONE METASTASES

In order for bone metastases to develop, cancer cells first have to metastasize to the bone marrow that is mainly composed of hematopoietic stem cells (HSCs) residing in 2 different biological structures known as osteoblastic and vascular niches.\textsuperscript{16} Communications between osteoblasts as well as other tumor stromal cells and HSCs are mainly driven through chemotaxative factors such as the stromal-derived factor 1 (SDF-1) on stromal cells and its receptor CXCR4 on HSCs.\textsuperscript{17}

Communication between the tumor cells and bone marrow HSCs is vitally important for the development of osseous metastases. A significant role in the interaction between cancer and bone is played by SDF-1 (also known as CXCL12) binding to CXCR4 with resultant CXCR4 signaling. The attachment/adherence of osteoclasts to bone/collagen is in large part the result of $\alpha_{i}\beta_3$. This is facilitated by cathepsin K exposing the RGD sequence from collagen to $\alpha_{i}\beta_3$. Osteoclast activation seems to contribute to osteolytic lesions erosions and pain. C-Src kinase activity is increased in response to integrin binding as well as RANKL–RANK interaction, and increased c-Src is involved in promoting osteoclast function/activation.

The development of bone metastases is a multistep process that includes the following sequence of events: (1) tumor growth, detachment of cancer cells, and invasion of the tissue stroma; (2) neoangiogenesis; (3) escape from the tissue by intravasation; (4) survival in the circulation; (5) chemotraction and arrest (docking and locking) in the bone marrow endothelial vessel wall; (6) extravasation; and (7) establishment of the metastatic microenvironment (osteoblastic metastasis) via the cross talk between the cancer and bone cells.\textsuperscript{18-21} Tumor cells achieve local bone resorption by chemotactically attracting osteoclast precursor cells (pre-osteoclasts) of the monocyte/macrophage cell line and stimulating their fusion and formation of mature osteoclasts. This osteoclastogenesis process is regulated by the nuclear factor kappa $\beta$ (NF-$\kappa\beta$) ligand (RANKL)–RANK–osteoprotegerin (OPG) system. RANKL is mainly expressed on the surface of osteoblasts, whereas its specific receptor (RANK) is expressed on osteoclast precursors. Stimulation of RANK by its ligand induces osteoclast formation and activation.\textsuperscript{22} The soluble glycoprotein OPG is a decoy receptor that binds to RANKL and thus inhibits RANKL–RANK interaction.\textsuperscript{21} OPG administration significantly reduces prostate cancer progression in bones because it inhibits tumor cell migration and bone resorption.\textsuperscript{21}

Secreteed urokinase plasminogen activator (uPA) binds to its receptor (uPA-R) on the surface of osteoblasts, activating proteolytic activity at sites adjacent to the osteoblasts and leading to local increase of proteolysis, because of either the direct protease activity of uPA or the indirect uPA-mediated generation of plasmin and subsequent activation of matrix metalloproteinases (MMPs).\textsuperscript{24-27}

PATHOPHYSIOLOGY OF BONE RESORPTION

Bone metastases may lead to pain via stimulation of nociceptors by algesic mediators (eg, cytokines, prostaglandin E, bradykinin, serotonin, substance P).

FIGURE 1. The spectrum of metastatic bone disease.

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Involvement of bone remodeling, invasion, or distortion, or compression of painful structures such as nerves, vasculature, and periosteum and microfractures of various joint structures may also lead to pain. Pain from osseous metastatic lesions may also occur from mechanical instability of “weakened bone” or high intraosseous pressures (>50 mm Hg).28

Although numerous contributing factors lead to the pain of osseous metastases, a significant portion of the pain seems to be related to osteoclastic bone resorption. Osteoclasts solubilize the mineral (e.g., hydroxyapatite) and degrade the organic matrix (e.g., type 1 collagen) with cysteine proteinases. The bone resorption occurs in an acidic microenvironment produced by proton secretion via vacuolar H⁺-ATPases in osteoclastic membranes. The first step in the process of bone resorption is that the osteoclast adheres to the bone surface. This adherence is mediated by specific membrane receptors. Podosomes are osteoclastic processes that become the primary attachment sites to the bone. The podosomes are made up of integrins and cytoskeletal proteins: actin microfilaments surrounded by vinculin and talin.29–30

The predominant attachment site is the vitronectin receptors (e.g., αvβ3 integrin), which recognizes the RGD (Arg-Gly-Asp) amino acid sequence in various bone matrix proteins (osteopontin, vitronectin, bone sialoprotein).29 Integrin activation appears to result in Pyk2-dependent recruitment of c-Src to the plasma membrane and lead to c-Src activation and association with Pyk2 and subsequent c-Src-dependent phosphorylation of the nonreceptor isoform of tyrosine phosphatase epsilon (cyt-PTPε) at its C-terminal residue Y638 and supports osteoclast adhesion and activation as well as proper structure, stability, and dynamics of podosomes.30

A highly convoluted membrane area termed the ruffled border and sealing zone appears in the osteoclast during bone resorption. The accumulation of podosomes at the bone surface occurs first with the ligand binding to the vitronectin receptor.29 Subsequently, a tight sealing zone is formed where osteoclastic acid and proteases reorganize elements to form a “double circle” of vinculin and talin around a core of F-actin.29

To effectively “digest” inorganic bone matrix components (e.g., hydroxyapatite), at least 2 major factors are needed: (1) acid (e.g., HCl) and (2) energy (e.g., adenosine triphosphate (ATP)). The osteoclasts generate H⁺ and Cl⁻ utilizing carbonic anhydrase II (CAIi) that catalyzes conversion of carbon dioxide [CO₂] and water [H₂O] into carbonic acid [H₂CO₃], which in turn dissociates into hydrogen ion [H⁺] and bicarbonate [HCO₃⁻].31,32 The HCO₃⁻ ions are then exchanged for Cl⁻ through the basolaterally located anion exchanger 2 (AE2),33,34 providing the Cl⁻ ions required for acidification [HCl] occurring in the resorption lacuna (Figure 2).

Inside the sealing zone, bone resorption is induced by active secretion of protons to the bone surface through a specialized vacuolar type ATPase (V-ATPase) requiring ATP, containing the a3 subunit35–38 and passive transport of chloride through the chloride channel [CIC-7], also to the bone surface (Figure 2).39–42 Hydrochloric acid lowers the pH to approximately 4.5, leading to dissolution of the inorganic matrix of bone.44

Thus, involvement of vacuolar H⁺-ATPase and carbonic anhydrase are crucial to “digesting” bone with subsequent creation of osteolytic lesions. c-Src may contribute to bone resorption, in part by (1) preventing the inhibitory effects of calcitonin on osteoclast function and facilitating osteoclast activation, (2) enhancing the normal organization of the osteoclast actin cytoskeleton and contributing to the formation of the “ruffled border” [after c-Src is recruited to the plasma membrane], (3) facilitating podosome activities by promoting a shift from stable focal adhesions with actin stress fibers to more dynamic podosome assemblies, (4) by phosphorylating cytochrome c oxidase within the mitochondria, thereby increasing cytochrome c oxidase activity, and subsequently contributing to the generation of high levels of ATP required for bone resorbing actions of osteoclasts (Figure 3).45–47 The ATP produced by c-Src-induced cytochrome c oxidase activity may be used by V-ATPase to provide energy for the proton pump to secrete hydrogen ions by the bone surface. Furthermore, the ATP generated may also contribute to nociception via binding to purinergic receptors (P2X2/3 and P2X3).

Cleavage of the type I collagen fibers is mainly mediated by the cysteine proteinase cathepsin K, which is

FIGURE 2. Osteoclastic bone resorption.

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active at low pH, and performs almost complete removal of the type I collagen fibers. The MMPs are also involved in the degradation of the organic matrix of the bones; however, their precise role remains uncertain (Figure 2). Targeting major processes involved in painful osseous metastases may lead to novel potential future therapeutic agents (Table 1).

Bone-residing metastatic cells are not directly able to destroy the hard bone tissue to enable them to survive and grow within the bone. Instead, they secrete paracrine factors, such as parathyroid hormone-related peptide and interleukin-6, which directly or indirectly stimulate osteoclast differentiation and activation.

**FIGURE 3.** c-Src and other signaling.

**Table 1.** Major processes that may be therapeutic targets for palliation of painful osseous metastases.

| Target | Process | Potential therapy |
|--------|---------|-------------------|
| CXCR4 | Communication (between tumor and hematopoetic stem cell) | CXCR4 antagonists |
| $\alpha_\beta_3$ | Attachment [between osteoclast ($\alpha_\beta_3$) and bone/collagen (RGD)] | $\alpha_\beta_3$ antagonists |
| Cathepsin K (exposes RGD) | Osteoclast activation | Cathepsin K inhibitors |
| RANKL–RANK interaction | Src prenylation | Denosumab |
| Src | | Bisphosphonates |
| Vacuolar H$^+\text{-ATPase}$ | Bone resorption—acidic microenvironment; proton secretion—dissolution of inorganic matrix | Inhibitor of vacuolar H$^+\text{-ATPase}$ [V-ATPase] (e.g. bafilomycin A1)—subunit $\alpha_3$ |
| Carbonic anhydrase | | Carbonic anhydrase inhibitors |
| CIC-7 (chloride channel) | | Inhibitors of CIC-7 (chloride channel) |
| Ae2 (anion exchanger) | | Inhibitors of Ae2 (anion exchanger) |
| Cathepsin K | Bone resorption; proteolysis—removal of collagen fibers | Inhibitors of cathepsin K |
| MMP-9 | | Inhibitors of MMP-9 |

The “standard” or “traditional” pharmacologic approach to the treatment or palliation of painful osseous metastases follows the World Health Organization (WHO)
an analgesic step ladder approach to pain relief. An international WHO Expert Committee on cancer pain, chaired by Dr Kathleen Foley of Memorial Sloan-Kettering Cancer Center, was convened in 1982, and in 1986 the WHO monograph Cancer Pain Relief was published. By 1993, it was translated into 22 languages. The WHO guidelines have been prospectively and cross culturally validated and shown to work well clinically. Zech et al published the largest prospective trial of WHO guidelines to date and achieved favorable pain control in 76% of 2118 cancer patients who were treated over a 10-year interval. Analgesic agents that may play a role in the WHO guidelines approach include: acetaminophen, traditional or nonselective nonsteroidal antiinflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, antidepressants, anticonvulsants, muscle relaxants, alpha-2 adrenergic agonists, N-methyl-d-aspartate receptor antagonists, and opioids/opioid-like analgesic agents.

The use of traditional (nonselective) NSAIDs in cancer induced bone pain has been questioned because of the lack of robust clinical evidence. The 2 randomized trials of NSAIDs in cancer pain do not separate out bone metastases, and 6 nonrandomized trials mention bone metastases but do not record incident pain. COX-2 inhibitors may in theory be of greater therapeutic potential in well-selected patients because of their antitumor/antiangiogenic properties. In an animal model of painful osseous metastases (POM), acute treatment with a highly selective COX-2 inhibitor attenuated both background and movement-induced pain, whereas chronic treatment additionally reduced tumor burden and osteoclast destruction. Prescribing NSAIDs necessitates careful patient selection and monitoring. Oral NSAIDs are associated with gastrointestinal, cardiovascular, renal, hematologic, and hepatic adverse events. Barkin et al published a comprehensive review of antiinflammatory drugs that cautioned prescribers to only use NSAIDs in older adults after careful selection because they are more likely to have cardiovascular disease, a natural age-related decline in renal function, and be taking multiple medications with potential NSAID interactions.

Lumiracoxib (Cyclooxygenase-189; Prexige) is a highly selective COX-2 inhibitor that is not approved in the United States, Canada, Australia, United Kingdom, and in some other countries because of the hepatic related adverse events. Compared with diclofenac, lumiracoxib has substantially reduced affinity for COX-1, being 300-fold less potent. The pH of lumiracoxib is 4.3 and thus, lumiracoxib is predicted to be more effective in a low pH environment; which may potentially be beneficial for pain relief in sites of metastatic bone lesions, where the local environment is acidic in nature. Buvanendran and Barkin have published a comprehensive review of lumiracoxib and its pharmacology.

It has been demonstrated in animal studies that gabapentin reverses dorsal horn changes associated with POM resulting in relief of spontaneous and movement related pain. Stimulated by favorable effects of gabapentin in animal models demonstrated modulation of continuous and stimulus-related bone pain and by observation that gabapentin is reported to be useful for the treatment of neuropathic cancer pain and as a synergistic adjuvant to opioid analgesics. Caraceni et al published an anecdotal report describing their treatment of 6 consecutive patients with incident pain caused by bone metastases with gabapentin not completely controlled by opioid medication. The addition of gabapentin was associated with significant clinical improvement of pain at rest and incident pain exacerbated by movement, which was sustained for up to 3 months. Gabapentin is a voltage-gated calcium channel blocker at the alpha-2-delta-1 subunit. Dosing may be guided by renal function because excretion of gabapentin is proportional to creatinine clearance/glomerular filtration rate. The bioavailability (F) is inversely and related to the dose as a function of absorption saturation.

Clinical trials have been underway for assessing the effects of pregabalin on attenuating chronic bone pain related to metastases. Pfizer began a multicenter (55 sites) double-blind randomized placebo-controlled trial of the efficacy and tolerability of flexibly dosed pregabalin in the treatment of cancer-induced bone pain but decided to discontinue additional enrollment into the NCT00381095 study effective September 5, 2010 after assessing the feasibility of completing study in a realistic time frame (there were no safety concerns). A double-blind randomized placebo-controlled trial of pregabalin versus placebo in conjunction with palliative radiotherapy (RT) for malignant bone pain (ISRCTN66947249) is currently still enrolling patients based in the United Kingdom. Pregabalin adverse events include weight gain, peripheral edema, QTc prolongation, thrombocytopenia, and central nervous system/neurologic events. Dosing is a function of renal creatinine clearance/glomerular filtration rate. It is conceivable that topiramate may be an antiepileptic drug that is particularly well suited for the treatment of painful osseous metastases because, in addition to its multiple mechanisms of action, it also possesses actions as a carbonic anhydrase inhibitor. Topiramate is a calcium channel blocker, sodium channel blocker, glutamic acid inhibitor; Gamma aminobutyric acid facilitator and may affect the N-methyl-d-aspartate receptor complex. Adequate hydration is recommended because of the...
BISPHOSPHONATES

Bisphosphonates are a class of drugs that target the process of bone resorption by inhibiting osteoclast function. Bisphosphonates may actually inhibit osteoclastic activity through stimulating OPG production (although that may only account for a small part of bisphosphonate actions). Early-generation bisphosphonates (ie, clodronate and etidronate) lack nitrogen and adhere to bone, where they are metabolized by osteoclasts. Metabolic products include cytotoxic ATP analogs that interfere with mitochondrial membrane potential and lead to osteoclast apoptosis. Later generation, nitrogen-containing bisphosphonates (ie, pamidronate, ibandronate, and zoledronate) inhibit osteoclasts by a different mechanism. They are internalized—but not metabolized—by osteoclasts, where they subsequently inhibit an enzyme called farnesyl pyrophosphate (FPP) synthase. FPP synthase is required for producing intermediates (eg, isoprenoid lipids) necessary for posttranslational modification (prenylation) of several small GTPases, including Ras, Rho, and Rac. These small GTPases are required for proper cellular vesicle transport, without which osteoclasts cannot form the tight sealing zones or ruffled borders at the bone surface that are required for resorption. Additionally, nitrogen-containing bisphosphonates may lead to the accumulation of isopentyl pyrophosphate that may be conjugated with adenosine monophosphate to form an endogenous ATP analog triphosphoric acid 1-adenosin-5'-ylster 3-(3-methylbut 3-eryl) ester [ApppI], which may inhibit mitochondrial adenine nucleotide translocase and cause osteoclast apoptosis. In the United States, bisphosphonates not used for osteoporosis include zoledronic acid (indicated for a range of solid tumors, with osseous metastases—breast, prostate, non–small cell lung, renal, and others), pamidronate (indicated for breast cancer and multiple myeloma), ibandronate (indicated for breast cancer), and clodronate (not approved in the United States).

Rapid-onset opioids approved by the Food and Drug Administration (FDA) in the United States include: oral transmucosal fentanyl citrate (Atiq), fentanyl buccal tablet (Fentora), fentanyl buccal soluble film (Onsolis), fentanyl sublingual spray (Subsys), and sublingual fentanyl (Abstral). Potential future rapid-onset opioids may include: intranasal fentanyl spray (Instanyl), fentanyl pectin nasal spray (Lazanda, Pec Fent; in Europe), and fentanyl dry powder intrapulmonary inhaler [TAIFUN]. Intravenous salmon calcitonin has been trialed in efforts to achieve analgesia from painful osseous metastases. Although there exist anecdotal reports of minor benefit, a larger prospective study demonstrated that intravenous calcitonin administered in a relatively high dose has a very limited therapeutic potential as an adjuvant analgesic in cancer patients with bone metastases. In 2003, Martinez et al performed a Cochrane Review and found that the limited evidence currently available for systematic review does not support the use of calcitonin to control pain from bone metastases. In 2006, they updated this Cochrane Review and reported the same findings.

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Topiramate may also cause paresthesias. One of the major classes of agents for the pharmacologic management of POM is that of opioid analgesics. Although long-acting opioids (eg, oxymorphone extended release) are used for “maintenance” therapy of baseline constant POM, rapid-onset opioids (ultra–short-acting opioids) may be particularly well suited to address episodes of breakthrough pain that tend to occur with advanced painful osseous metastases. Rapid-onset opioids approved by the Food and Drug Administration (FDA) in the United States include: oral transmucosal fentanyl citrate (Atiq), fentanyl buccal tablet (Fentora), fentanyl buccal soluble film (Onsolis), fentanyl sublingual spray (Subsys), and sublingual fentanyl (Abstral). Potential future rapid-onset opioids may include: intranasal fentanyl spray (Instanyl), fentanyl pectin nasal spray (Lazanda, Pec Fent; in Europe), and fentanyl dry powder intrapulmonary inhaler (TAIFUN).

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Multiple studies have demonstrated the efficacy of bisphosphonates in reducing skeletal complications and pain from bone metastases. Intravenous zoledronic acid has demonstrated the broadest clinical activity. Zoledronate (zoledronic acid) is the most potent of the nitrogen containing bisphosphonates, displaying superior efficacy in inhibiting FPP synthase activity, reducing bone resorption, and relieving pain compared with other bisphosphonates, such as clodronate and pamidronate. Zoledronic acid is the only bisphosphonate that has statistically shown significant reductions in skeletal morbidity, including bone pain, in patients with metastatic prostate cancer. Fulfar et al demonstrated a relationship between a decrease in bone pain in 75% of patients, and modification of C-telopeptide levels was identified in bone metastases from prostate cancer treated with zoledronic acid. Zoledronate, in particular, has been reported to have direct antitumor properties in preclinical studies. It is capable of inducing tumor cell apoptosis, inhibiting cancer cell invasion, and limiting metastatic outgrowth in visceral tissues at extremely high doses. Zoledronate treatment has been associated with a decline in circulating levels of the potent proangionic molecule, vascular endothelial growth factor, in cancer patients. Zoledronate-mediated reductions in vascular endothelial growth factor levels were associated with increased time to a skeletal-related event, increased time to the progression of bone disease, and longer time to the worsening of performance status. Zoledronic acid distributes and bonds to osseous tissues and has a triphasic postinfusion decline process with
a terminal half-life of 146 hours. Before initiation of therapy using zoledronate, a dental evaluation and subsequent follow-up are needed in efforts to monitor for the occurrence and risk of osteonecrosis of the jaw.

Saad et al\textsuperscript{99} initiated a randomized placebo-controlled trial of 422 prostate cancer patients and demonstrated that zoledronic acid significantly reduced the rate of SREs. Similar results have been described in patients with other types of tumor such as lung cancer.\textsuperscript{100} Furthermore; zoledronic acid has been demonstrated to be superior to pamidronate in reducing skeletal complications in a randomized trial of 1130 breast cancer patients.\textsuperscript{101} Zoledronic acid can cause flu-like symptoms that are manageable with standard treatment. Renal monitoring is recommended due to association with iatrogenic renal function deterioration. Use of zoledronic acid should be avoided in patients with a creatinine clearance of $\leq 30$ mL/min and caution should be used when using zoledronate in patients with other nephrotic agents. Dose reductions should be followed according to the package information sheet for patients with renal dysfunction. Long-term use of bisphosphonates is also associated with a small risk of osteonecrosis of the jaw.\textsuperscript{102}

\section*{COLLATERAL NONOPIOID/NSAID ANALGESIC PHARMACOTHERAPY AND INITIATIVES FOR COMPREHENSIVE CARE}

It is highly predictable that patients suffering from painful bony metastases may experience comorbid anxiety (generalized anxiety disorder) and depression (major depressive disorder) as a function of this debilitative painful disease process. Such patients may benefit from pharmacotherapy approved for this psychopathology (ie, generalized anxiety disorder and major depressive disorder) and 3 pain syndromes (diabetic peripheral neuropathic pain, fibromyalgia syndrome, and chronic musculoskeletal pain). The multiple FDA approvals of duloxetine may help preserve self-esteem especially in those patients who deny the pain-related depression and/or anxiety, and thus, may refuse a typical antidepressant or anxiolytic. Additionally, these patients may benefit from psychotherapy and physical therapy management components. The available analgesic therapy should be patient-specific, patient-focused, and patient-centered personalized care.\textsuperscript{103,104} Comprehensive care interventions for chronic pain may facilitate an augmented functional recovery, enhancing both physical and mental health and further promoting resilience and responsiveness to pain and collateral stressors.

Cognitive behavior therapy and techniques promoting patient coping skills may be beneficial in this regard.

\section*{HORMONAL APPROACHES TO THE MANAGEMENT OF POM}

Only certain types of cancers (eg, breast cancer, prostate cancer) may respond in some fashion to hormonal therapy. Intuitively, it would seem that any hormonal therapy that achieves antineoplastic results may also possess antinociceptive qualities under certain circumstances. An example of a cancer type that may respond to hormonal therapy is prostate cancer. Androgen deprivation therapy is achievable with surgical castration (bilateral orchiectomy), or medical castration that may include agents such as: synthetic gonadotropin-releasing hormone (GnRH) agonists [eg, leuprolide, buserelin, goserelin, histrelin, and triptorelin—in phase II trials—also a 60-month formulation triptorelin embonate is under development], cytochrome P450 enzyme 17A1 (CYP17A1) inhibitors (inhibition of androgen synthesis) (eg, nonselective CYP17A1 inhibitors), ketoconazole (aromatase inhibitors, aminoglutethimide), selective CYP17A1 inhibitors (abiraterone acetate—in phase III clinical trials, TOK-001 and TAK-700 in phase I/II trials), androgen receptor antagonists (eg, bicalutamide, nilutamide, flutamide) and (MDV 3100—in phase III clinical trials, BMS-649988 in phase I clinical trials), inhibitors of 5a-reductive (which converts testosterone to the more potent dihydrotestosterone, eg, finasteride, dutasteride), as well as other agents such as GnRH blockers (eg, degarelix—in phase III trials, not associated with concomitant clinical flare from testosterone surge that may occur with GnRH agonists), glucocorticoids (steroidogenesis suppressive agents), and estrogen (eg, diethylstilbestrol—suppress steroidogenesis by decreasing luteinizing hormone—releasing hormone secretion and indirectly affecting pituitary luteinizing hormone production).\textsuperscript{105,106}

The clinical effects of flare can be limited by concomitant antiandrogen treatment (eg, flutamide or bicalutamide),\textsuperscript{107} which acts to inhibit the stimulatory effect of the testosterone surge by blocking testosterone binding to androgen receptors in prostate cancer cells. However, this strategy is not always effective and antiandrogens are also associated with additional side effects.\textsuperscript{108,109} Other pharmacological endocrine options for prostate cancer include the use of estrogens, antiandrogen monotherapy, and complete androgen blockade using an antiandrogen plus a GnRH receptor agonist.\textsuperscript{110} However, these approaches are used infrequently in practice because of concerns about the efficacy and/or
side effects, which can include cardiotoxicity, gynecomastia, breast pain, and liver toxicity.\textsuperscript{110}

Phase III trial data for the recently approved GnRH receptor blocker, degarelix, demonstrated that it is as effective and well tolerated as GnRH agonists. It has a pharmacological profile more closely matching orchiectomy, with an immediate onset of action and faster testosterone and prostate-specific antigen suppression, without a testosterone surge or microsurges after repeated injections. As a consequence, with this GnRH blocker, there is no risk of clinical flare and no need for concomitant antiandrogen flare protection and very low histamine release.\textsuperscript{111}

There is now incontrovertible evidence that castration-resistant prostate cancer (CRPC) remains hormone driven, with intratumoral steroid synthesis and subsequent androgen receptor signaling, fueling tumor growth.\textsuperscript{112} Several novel agents targeting androgen receptor signaling are currently being evaluated including abiraterone and MDV3100. A phase III trial of abiraterone acetate in post-docetaxel patients has shown an overall survival benefit in advanced CRPC.\textsuperscript{113} MDV3100 is an androgen receptor antagonist that blocks androgens from binding to the androgen receptor and prevents nuclear translocation and coactivator recruitment of the ligand–receptor complex, as well as inducing tumor cell apoptosis, and has no agonist activity. Scher et al\textsuperscript{112} recorded encouraging antitumor activity with MDV3100 in patients with CRPC.

**RADIOTHERAPY**

External beam RT for osseous metastases may lead to improved analgesia, elimination or reduction of analgesic usage, functional improvement, such as increased ambulation, and reduction in the risk of fracture in weight-bearing bones. Large multi-institutional randomized trials conducted by the Radiation Therapy Oncology Group have demonstrated that 80\% of patients receiving RT for osseous metastases will experience complete to partial pain relief, typically within 10–14 days of the initiation therapy.\textsuperscript{114} A correlation was also found between the incidence of pain relief and the site of bone metastases, in that a lower response was shown in limb localizations.\textsuperscript{115}

Approximately 80\% of patients may be successfully treated with sequential whole skeleton radiation, in which 6–8 Gy is administered as a single fraction to either the upper and lower part of the body, followed by a second dose of 6–8 Gy, given 4–6 weeks later, to the remainder of the body.\textsuperscript{116} Most prospective randomized trials evaluating differences in the outcomes have shown that single fraction regimens (mostly 8 Gy) are at least equal in analgesic efficacy to the various fractionated regimens.\textsuperscript{117} These results have been confirmed in 3 metaanalyses.\textsuperscript{118–120} Wu et al\textsuperscript{118} included 8 randomized trials (3260 patients) in a metaanalysis, comparing 1 × 8 Gy single fraction RT with various multifraction regimens and found that all multifraction regimens were essentially equal to single fraction therapy.

Similar results have been observed in the metaanalysis of Sze et al,\textsuperscript{119} which included 3621 patients from 12 randomized trials. The complete response rates were 34\% (508/1476) after single fraction RT and 32\% (475/1473) after multifraction RT (odds ratio (OR), 1.10; 95\% confidence interval (CI), 0.94–1.30, \(P > 0.05\)). Overall response rates were 60\% (1080/1814) and 59\% (1060/1807), respectively (OR, 1.03; 95\% CI, 0.90–1.19; \(P < 0.05\)).\textsuperscript{119,121} Chow et al\textsuperscript{120} included 5000 patients from 16 randomized trials in their metaanalysis. The overall response rates (intention-to-treat analysis) were 58\% (1468/2513) after single fraction RT (mostly 1 × 8 Gy) and 59\% (1466/2487) after multifraction RT (mostly 5 × 4 Gy or 10 × 3 Gy) (OR, 0.99; 95\% CI, 0.95–1.03; \(P = 0.60\)).\textsuperscript{120,121}

**RADIOPHARMACEUTICALS**

Radiopharmaceuticals provide several advantages over conventional external beam RT: (1) they can be administered intravenously, (2) they can treat multiple diffuse sites with mild bone marrow depression, and (3) they cause fewer adverse side effects such as nausea, vomiting, diarrhea, and tissue damage.\textsuperscript{14} Radiopharmaceuticals are relatively easy to administer but should be performed by clinicians appropriately trained in nuclear medicine. Although the preparation and steps for each patient surrounding radiopharmaceutical administration is different and should be individualized, certain common treatment guidelines exist (Table 2). Absolute contraindications for using radiopharmaceuticals include pregnancy and patient refusal. Relative contraindications require careful consideration of risks versus potential benefits within the context of the patients’ wishes (Table 3).\textsuperscript{14} Multiple radiopharmaceuticals exist, which may provide analgesia from painful osseous metastases; some agents have appropriate energies to be imaged as well (Table 4).

Figuls et al\textsuperscript{122} updated a Cochrane Review to determine efficacy and safety of radioisotopes in patients with painful bone metastases. Their update includes 15 studies (1146 analyzed participants): 4 (325...
participants) already included and 11 new (821 participants). They found a small benefit of radioisotopes for complete relief [risk ratio (RR), 2.10; 95% CI 1.32–3.35; number needed to treat to benefit (NNT) = 5] and complete/partial relief (RR, 1.72, 95% CI, 1.13–2.63; number needed to treat to benefit = 4) in the short and medium term (8 studies, 499 participants). Leukocytopenia and thrombocytopenia are secondary effects significantly associated with the administration of radioisotopes (RR, 5.03; 95% CI, 1.35–18.70; number needed to treat to harm = 13). Pain flares were not higher in the radioisotopes group (RR, 0.74; 95% CI, 0.27–2.06).122

### Table 2. Treatment guidelines.

| Procedure                                                                 |
|---------------------------------------------------------------------------|
| Complete history and physical (with thorough neurological examination)    |
| Review bone scan; check for increased uptake (hot spots) at painful areas |
| Complete blood counts                                                    |
| Perform renal studies (minimal blood urea nitrogen/creatinine)            |
| Acquire informed consent                                                  |
| Hydrate patient                                                           |
| Double check that patient is suitable candidate for therapy              |
| Complete blood counts every other week after injection for 3 months or recovery to baseline counts (generally, the usual hematologic response is a 20%–30% decrease in platelet count with a nadir in about 5–6 weeks and recovery by 12 weeks) |
| Maintain a close patient follow-up postinjection                          |
| Change an aspirin products (including traditional NSAIDs) to COX-2 selective inhibitors (eg, celecoxib) |
| Have the patient keep a diary postinjection with daily entries including evening temperature, 0–10 pain score (numerical rating scale-11), and side effects (nausea, etc.) |

### Table 3. Contraindications for treatment of painful osseous metastases with radiopharmaceuticals.

| Condition                                                                 |
|---------------------------------------------------------------------------|
| White blood cell count <2500                                              |
| Platelet count <60,000 (stable)                                           |
| Recent rapid fall in platelet count (even if over 60,000)                 |
| Disseminated intravascular coagulopathy                                  |
| Myelosuppression chemotherapy within 1 month                             |
| Hemibody radiotherapy within 2 months                                    |
| Extensive soft tissue metastases                                         |
| Pregnancy                                                                 |
| Patient refusal                                                           |
| Inability of patient to follow radiation safety precautions              |
| Impending spinal cord compression or pathological fracture               |
| Estimated survival time <2 months                                        |
| Karnofsky performance <50                                                |
| Significant renal insufficiency                                          |

Strontium-89 chloride

Strontium is a divalent cation, like calcium, and is incorporated into hydroxyapatite in the bone after intravenous injection and is a bone-specific radioisotope. Sr-89 chloride (89Sr; Metastron; GE Healthcare Global, Bucks, United Kingdom) was the first FDA-approved radiopharmaceutical for bone pain palliation.123 89Sr is a calcium analog, which is preferentially deposited in the osseous tissue.124 Approximately 10-fold more 89Sr is absorbed by bone metastases than by bone marrow.124 89Sr is a beta emitter with the longest half-life of the radiopharmaceutical agents clinically available for treatment of painful osseous metastases. It is also the most used radiopharmaceutical. 89Sr has a very low yield gamma emission, which makes it unsuitable for imaging. It is rapidly cleared from the blood via renal excretion and incorporation into bone mineral.125,126 The suggested dose is 0.04 mCi/kg or 4 mCi per patient.125,126

Pain relief usually begins within 2 weeks of treatment, with maximum benefit by 6 weeks, and lasts between 4 and 15 months.125,126 Mild thrombocytopenia or leukopenia may occur in up to 80% of patients.125,126 Platelets decline approximately 15%–30% below pretreatment levels and usually completely recover in 2–3 months, enabling repeat treatment at that time.125,126 Occasionally, recovery of platelet count to baseline may take about 6 months.125,126 In addition, 15%–20% reductions in white blood cells have also been recorded after 89Sr administration.125 A transient flushing sensation immediately after rapid 89Sr injection has been noted and is self limited. Bone pain may transiently increase in some patients (≤20% reported).

Kraeber-Bodere et al127 used a different approach in the evaluation of Sr-89 efficacy. They examined the relationship of therapeutic response and the degree of bone involvement and flare phenomena in patients with metastatic prostate cancer who were treated with Sr-89. They evaluated 94 patients (117 injections of 4 mCi) and compared the efficacy of treatment according to the extent of bone involvement (moderate and extensive). An improvement in the quality of life was obtained in 65% of cases, a decrease in pain in 78% (31% complete responses), and a reduction in analgesic use in 60%. Efficacy was
significantly better for pain decrease \( (P = 0.005) \) and reduction of analgesic use \( (P < 0.0035) \) in patients with moderate bone involvement than in patients with extensive osseous disease.\(^{127}\)

A recent systematic review of the available literature published by Finlay et al.\(^{128}\) showed a percentage of complete responders to Sr-89 ranging from 8% to 77%, with a mean value of 32%, and no responders ranging from 14% to 52% (mean, 25%). In general, 44% of patients had some degree of response to Sr-89 treatment, giving a mean overall response of 76%.\(^{128}\)

Phosphorus-32 orthophosphate (chromic phosphate P32)

Friedell and Storaasli\(^ {129}\) began treating patients with widespread painful osseous metastases in 1942 and found that 83% had significant palliation of pain. The uptake of 32P in bone is avid because phosphorous, along with calcium and hydroxyl, is a component of the hydroxyapatite crystal. The average tissue penetration is 2–3 mm (maximum 8 mm) after intravenous administration.\(^ {130}\) Also, it is a pure beta emitter, and therefore cannot be imaged.\(^ {130}\) With its high maximum energy of beta emission, it offers the greatest risk of bone marrow depression, and therefore, is hardly ever used for palliation of painful osseous metastases. All (acute lymphocytic leukemia) risk development has been reported with use.

Samarium-153 lexidronam

Samarium-153 lexidronam \([153\text{Sm}–\text{ethylene diamine tetramethylene phosphonic (EDTMP)}]\) was originally described by William Goeckler in 1984, and it was approved by the Federal Drug Administration (FDA) on March 28, 1987 for relief of pain in patients with osteoblastic bone metastases.\(^ {131,132}\) 153Sm-EDTMP is a stable complex of radioactive samarium-153 and EDTMP.\(^ {133–136}\) Favorable features of this bone-specific radioisotope 153Sm-EDTMP include a short physical half-life, which allows for efficient handling and fractionated dosing; gamma emission of 103 keV, which is good for scintigraphic imaging; low tissue penetration, which reduces the risk of radiotoxicity to bone marrow; very low in vivo degradation; and no liver or other soft tissue uptake.\(^ {6,133,135}\) The recommended dose is roughly 1.0 mCi/kg intravenously administered over 1 minute.\(^ {124–127}\) The onset of analgesia is approximately 48 hours to 7 days.\(^ {133–136}\) Repeated doses can be administered, if necessary, at least 6–8 weeks after the first dose.\(^ {133–136}\)

The group lead by Sartor et al.\(^ {137}\) reported the safety and efficacy of repeated doses of Sm-153 in patients with metastatic bone pain.\(^ {137}\) Significant decreases in pain scores \( (P < 0.002) \) were observed at week 4 after each of the first 3 doses and maintained at week 8 after the first 2 doses \( (P < 0.003) \) but not after the third dose. Decreases in pain scores were observed in 70%, 63%, and 80% of patients, respectively, at week 4 after the first 3 administrations. The available data prove that repeated treatment with Sm-153 is both safe and effective in patients with metastatic bone disease.

The alpha-emitter 223Ra-based alpharadin is a new radiopharmaceutical under development by Algeta ASA in collaboration with Bayer Schering Pharma AG.\(^ {138}\) Early clinical data demonstrated that median time to prostate-specific antigen progression, median survival, and pain relief were superior to placebo, without dose-limiting hematologic toxicity.\(^ {138}\)

**INTERVENTIONAL APPROACHES TO THE MANAGEMENT OF POM ABLATION**

**Patient selection for ablation**

Patients may be offered focal ablative therapy (RFA or cryoablation) for painful metastases when 3 factors are present. First, a patient reports moderate or severe pain, typically \( \geq 4 \) of 10 for worst pain in a 24-hour period. Second, a patient’s local pain is limited to 1 or 2

Table 4. Characteristics of radiopharmaceuticals for the treatment of POM.

| Radiopharmaceuticals | Half-life, days | Beta energy, MeV (max) | Gamma energy, keV | Usual dose |
|----------------------|----------------|------------------------|-------------------|-----------|
| Phosphorous-32 phosphate | 14.3 | 1.7 | 0 | 5–10 mCi |
| Strontium-89 chloride | 50.5 | 1.5 | Essentially none | 4 mCi |
| Samarium-153 lexidronam | 1.9 | 0.8 | 103 | 1 mCi/kg |
| Rhenium-186 hydroxyethylidene diphosphonate* | 3.8 | 101 | 137 | 35 mCi |

*Not approved in the United States.
sites and the patient’s pain is associated with a corresponding abnormality evident with cross-sectional imaging. Third, treatment of the patient’s painful metastatic lesion must be amenable to the use of ablative devices. Lesions that are amenable to ablative therapy are typically osteolytic or mixed osteolytic/osteoblastic in nature or otherwise composed of soft tissue. Exclusion of patients from focal ablative therapy usually occurs when one or more of the following situations are present. First, if a successful treatment requires the treatment of a portion of the lesion located within 1 cm of the spinal cord, major motor nerve, brain, artery of Adamkiewicz, bowel, or bladder. 

Although cryoablation may effectively treat intact or sclerotic bone, RFA energy is poorly delivered into sclerotic or otherwise intact bone. Cryoablation may have several other unique advantages over RFA for treatment of pain as a result of metastatic disease. Importantly, the zone of ablation is readily monitored with intermittent computed tomography or magnetic resonance imaging. The ice ball that is generated appears as a low attenuation region with a well-defined margin with CT and with various pulse sequences with MR imaging. Cryoablation also allows the simultaneous use of multiple cryoprobes, which allows complete ablation of large lesions (up to approximately 8-cm diameter) in a single session. This approach avoids leaving residual neoplasm between the separate cryoprobes that is possible between sequential single overlapping ablations. Furthermore, cryoablation may treat larger lesions than RFA because the site of the ice ball generated is generally larger than the tip of the radiofrequency probe.

VERTEBRAL AUGMENTATION PROCEDURES

The incidence of spinal metastases and vertebral compression fractures continues to rise, with associated axial pain, progressive radiculomyelopathy, and mechanical instability. Vertebral augmentation procedures such as percutaneous vertebroplasty and percutaneous kyphoplasty can provide relief in patients with pathologic vertebral body compression fractures that do not cause neurological deficits but severely compromise quality of life largely because of intractable pain and also because of loss of independence, mobility, and function often with resulting isolation/loneliness.

Vertebroplasty

Percutaneous vertebroplasty, first described in 1987, is a radiologically guided procedure in which percutaneous injection of polymethylmethacrylate, a surgical bone cement, is injected into a vertebra under imaging guidance.

Indications

The goal of percutaneous vertebroplasty is to provide pain relief and bone strengthening in painful vertebral body compression fractures. Selected patients should have focal, intense, and intractable midline spinal pain at the level of, or within 2 vertebral levels below, the fracture, without evidence of definite radicular signs and symptoms, and have failed conservative management.

Contraindications

The absolute contraindications to percutaneous vertebroplasty are bleeding disorder, unstable fracture as a result of posterior element involvement, and a lack of a definable level of vertebral collapse. Relative contraindications include patient inability to lie prone for the expected procedure duration (1–2 hours), lack of surgical back-up or patient monitoring facilities, and the presence of neurological signs and symptoms caused by vertebral body collapse or tumor extension. Very severe vertebral compression may be technically difficult but is not a contraindication to the procedure.

An 11- or 13-gauge needle is passed along an anesthetized tract percutaneously and used to penetrate the cortex of the vertebra using a transpedicular, parapedicular, or costopedicular approach. Polymethylmethacrylate cement is then instilled under close imaging guidance until the anterior two-thirds of the vertebral body is filled and the cement is equally distributed on both sides.

Lee et al. reported on 19 percutaneous vertebroplasty procedures performed mainly in breast, prostate, lung, and renal cancers. Of these 19 cases, 10 patients (53%) were treated for solitary lesions, 3 (16%) were injected at 2 levels, and the remaining 6 cases (31%) underwent cement injection at 3 levels. The majority of individuals (84%) reported short- and long-term symptomatic improvements.

Saliou et al. evaluated a total of 74 vertebrae in 51 patients, (22 women and 29 men) with a mean age of 62.5 years with malignant fractures of the spine with epidural involvements. They concluded that percutaneous vertebroplasty provided effective analgesia in patients experiencing pain related to malignant spinal tumors with epidural extension and was associated with a relatively low complication rate.

Mikami et al. conducted a retrospective (2002–2008) review of 141 painful vertebral metastases treated with percutaneous vertebroplasty using
polymethylmethacrylate. The mean preoperative visual analog score (VAS) score was 7.3, that significantly improved to 1.9 postoperatively (at discharge), with a mean improvement rate of 73.3%. Regarding complications, no new fractures of adjacent vertebral bodies were encountered, but asymptomatic cement leakage was seen in 49% of the patients.148

Chew et al149 performed a systematic review of the safety and efficacy of percutaneous vertebroplasty in malignancy. Pain reduction ranged between 47% and 87%. The risk of serious complications was significant, ranging up to 2%.149

**Kyphoplasty**

Kyphoplasty has evolved from vertebroplasty and aims to offer the benefit of analgesia in vertebral fractures in combination with restoration of vertebral body height. A balloon-like device is inflated, which restores vertebral body height and creates a cavity into which the cement is then injected.145

Qian et al150 performed a retrospective review of clinical outcome data for 48 patients with multiple spinal metastases treated with kyphoplasty. Outcome data (vertebral body height variation, degree of kyphosis, VAS score for pain, Oswestry Disability Index score, the Short Form-36 questionnaire score for function) were collected preoperatively, postoperatively, and at 1 month, 6 months, 1 year, and 2 years after treatment. Significant improvements in all the outcome measures were observed postoperatively and throughout the duration of follow-up. The mean anterior vertebral body height variation improved from 52.7% ± 16.8% preoperatively to 85.3% ± 13.2% postoperatively (P < 0.001). Kyphotic angle improved from 16.4 ± 4.7 degrees preoperatively to 8.4 ± 2.5 degrees postoperatively (P < 0.001). The mean VAS score decreased significantly from presurgery to postsurgery (7.4 ± 2.1 to 3.8 ± 1.6; P < 0.001), as did the Oswestry Disability Index score (71.5 ± 16.7 to 32.4 ± 9.6; P < 0.001). The Short Form-36 scores for bodily pain, physical function, vitality, and social functioning all also showed significant improvement (P < 0.05). Qian et al150 concluded that kyphoplasty appears to be an effective, minimally invasive procedure for the stabilization of pathological vertebral fractures caused by metastatic disease, even in levels with vertebral wall deficiency. The kyphoplasty procedure may lead to a statistically significant reduction in pain, improvement in function and possibly the prevention of further kyphotic deformity of the spine.150

**INTRATHECAL THERAPIES FOR POM**

The use of intrathecal analgesics is an important treatment consideration for many patients with chronic cancer pain.151 Intrathecal analgesia has emerged as a key therapeutic option for pain relief for patients who have failed other treatment avenues as well as patients with adequate analgesia on high-dose enteral or parenteral therapy but with unacceptable side effects.152

Smith et al153 performed a multicenter, randomized prospective trial evaluating intrathecal drug delivery for 202 cancer patients. Specific outcomes from the study of Smith et al were that opioid-induced toxicities such as fatigue, sedation, and cognitive slowing were improved compared with patients receiving comprehensive medication management. Pain scores were also improved with respect to baseline and compared with the scores in patients receiving comprehensive medication management, with nearly two-thirds of intrathecal drug delivery system patients having scores in the target range of less than 4/10. The number of intrathecal drug choices is limited and should be guided by consensus guidelines.154 First-line intrathecal analgesics include morphine, sulfate, hydromorphone, and ziconotide154; however, there are other alternative agents as well.151,152,154 Appropriate selection of patients with intractable cancer pain for chronic intrathecal analgesia therapy is paramount155 and clear communication of the rationale for infusion is very important, as is regular education about infusion management.156

**POSSIBLE FUTURE APPROACHES TO THE MANAGEMENT OF POM**

**Inhibitors of the RANK–RANKL system**

The RANK–RANKL system plays a fundamental role in the maturation and function of osteoclasts and thus in the development and progression of bone metastasis. Therefore, inhibition of this system has been evaluated as therapeutic target for the treatment of osteolytic diseases, including bone metastasis.15

It seems that some of the pain from metastatic bone lesions may be secondary to the effects of osteoclastic activity, so that “shutting down” osteoclastic activity is paramount to incorporate in analgesic treatments. Osteoclast bone resorbing activity is dependent on the binding of the tumor necrosis factor (TNF) family molecule OPG ligand (OPGL),157 which is expressed
on activated T cells and osteoblasts, to a receptor termed receptor activator of nuclear factor kappa β, abbreviated RANK.157 RANK is expressed on osteoclast precursors and mature osteoclasts.22 Any treatment that impedes the OPGL–RANK interaction will impair RANK activation and therefore impair osteoclastic activity and bone resorption. OPGL is a soluble TNF receptor molecule that is secreted and binds to the RANK activating site of OPGL, acting as a “dummy” or “decoy” receptor and preventing OPGL from binding to and activating the osteoclast RANK receptor (Figure 2).157–159

Amgen created a recombinant Fc-OPG (AMGN-0007) to treat multiple myeloma and bone metastatic breast cancer. Results from the phase I trial were encouraging, in that Fc-OPG was well tolerated and its inhibitory effects on bone resorption were similar to the bisphosphonate, pamidronate.160 However, because of the superior efficacy of their newer agent, denosumab (AMG-162)—a fully human monoclonal antibody that specifically neutralizes RANKL—at inhibiting bone resorption, and concerns regarding deleterious OPG-mediated protection from TNF-related apoptosis-inducing ligand-mediated apoptosis in cancer cells, Amgen ceased further clinical development of AMGN-0007.161

Fizazi et al162 compared the efficacy of 2 doses of denosumab (180 mg every 4 weeks or 180 mg every 12 weeks) with continued intravenous bisphosphonate treatment (zoledronic acid or pamidronate) in reducing bone turnover and the incidence of SREs. Patients on the highest dose of denosumab were less likely to have SREs compared with patients on intravenous bisphosphonates in 175 days while on trial (2/38 of the denosumab group vs. 6/35 of the bisphosphonate group). High doses of denosumab also induced a 78% decrease in urine levels of N-telopeptide of type I collagen (uNTx), a marker of bone turnover, compared with a 33% reduction in the continuous bisphosphonate-treated group.162

The US Food and Drug Administration approved denosumab (Xgeva) on November 19, 2010 to help prevent SREs in patients with cancer that has spread (metastasized) and damaged the bone (SREs include bone fractures from cancer and bone pain requiring radiation). Denosumab is not approved for patients with multiple myeloma or other cancers of the blood. Denosumab’s safety and effectiveness were confirmed in 3 randomized, double-blind clinical studies in 5723 patients comparing denosumab with zoledronate. One study involved patients with breast cancer, another in patients with prostate cancer, and a third included patients with a variety of other cancers. The studies were designed to measure the time until occurrence of a fracture or spinal cord compression as a result of cancer or until radiation or surgery for control of bone pain was needed. In patients with breast or prostate cancers, denosumab was superior to zoledronate in delaying SREs. In men with prostate cancer, the median time to an SRE was 21 months with denosumab compared with 17 months with zoledronate.

A phase II study in patients with breast cancer bone metastasis not previously treated with bisphosphonates revealed that denosumab suppressed the uNTx levels to an extent similar to intravenous bisphosphonates. Importantly, the drug was well tolerated and the risk of SRE was reduced.163

A phase III, randomized double-blind study that compared denosumab with zoledronate for the treatment of breast cancer patients with bone metastases revealed that denosumab was superior for delaying or preventing SREs, whereas the overall SRE incidence, the renal toxicity, the osteonecrosis of the jaw, and the overall survival were similar.164

An example of bone biomarker use as an end point is provided by a phase 2 study in patients who were being treated with zoledronic acid, but whose NTX levels remained more than 50 nmol·L⁻¹·mmol⁻¹·creatinine. Denosumab was able to reduce NTX levels to less than 50 nmol·L⁻¹·mmol⁻¹·creatinine in a significantly greater proportion of patients than those who continued with zoledronic acid.162 Bone biomarkers may also be valuable in directing therapy as in the BISMARK study, which compares standard dosing of ZOL 4 mg intravenous every 3–4 weeks versus a marker directed schedule based on updated levels of NTX.165

Cleeland et al166 elsewhere examined differences between the 2 treatments in patient-reported pain interference with daily functioning using data from a phase 3 trial that compared denosumab with zoledronic acid in women with advanced breast cancer and bone metastases; and their findings in December 2010 presented at the 33rd annual San Antonio Breast Cancer Symposium.

In the trial, patients completed the 11-point Brief Pain Inventory-Short Form to assess pain interference with general activity, walking, work, mood enjoyment of life, relations with others, and sleep and to assess pain severity. The analysis included 1018 patients treated with denosumab and 1011 patients treated with zoledronic acid. Results showed that time to improvement in pain interference with activity (PIWA) tended to occur more rapidly with denosumab than with zoledronic acid (a median of 70 vs. 86 days; $P = 0.09$). Also, time to worsening PIWA tended to be longer with denosumab than with zoledronic acid (median of 394 vs. 310 days; $P = 0.13$). In women with no pain or only mild pain at enrollment, denosumab showed
a trend for shorter time to improvement in PIWA and a longer time to worsening PIWA. Also, a shift in analgesic use from no or low analgesics to strong opioids occurred in fewer patients treated with denosumab.

**Cathepsin K inhibitors**

Cathepsins are a class of globular lysosomal proteases that belong to the papain-like cysteine protease family. Cathepsin K represents the key enzyme responsible for osteoclastic bone resorption actively participating in the process of bone turnover. This cysteine protease plays a key role in bone matrix degradation and seems to be a limiting step in osteoclastic bone resorption. Cathepsin K is highly expressed in osteoclasts and is responsible for the cleavage of the helical and telopeptide regions of bone collagen (collagen type I). By degrading collagen I, cathepsin K not only promotes the destruction of a major constituent of the bone extracellular matrix, it also exposes cryptic RGD motifs in collagen, which are essential for osteoclast adhesion to the extracellular matrix. Several cathepsin K inhibitors, including MK-0822 (odanacatib), AAE581 (balicatib), ONO-5334, and SB462795 (relacatib), are currently in clinical trials for osteoporosis, osteoarthritis, and neoplastic bone metastasis. A cathepsin K inhibitor was demonstrated to reduce the size of osteolytic lesions by 66% when used in a preclinical treatment protocol (inhibitor administered 18 days after tumor cell inoculation) and by 61% when used in a prevention protocol (inhibitor administered at the same time as tumor cell inoculation). Because of the adverse effects in the skin, clinical development of all cathepsin K inhibitors, except for odanacatib have been suspended.

Odanacatib significantly reduced markers of bone resorption in healthy postmenopausal women. A phase II controlled study, in which women with bone metastatic breast cancer were given daily doses of odanacatib or a single dose of zoledronic acid, has been completed. In this study, both patient groups experienced similar reductions in markers of bone turnover, including uNTx levels. Inhibitors of cathepsin K effectively suppress bone resorption in animal models. Cathepsin K inhibitor (L-006235) showed to reduce the size of osteolytic lesions by 66% when administered 18 days after tumor cell inoculation and by 61% when administered at the same time as tumor cell inoculation. A phase II controlled study on women with breast cancer metastatic to bone randomized to receive daily administration of odanacatib (5 mg) or a single 4 mg intravenous dose of zoledronic acid showed bone remodeling markers reduction (urinary NTx) after 4 weeks of treatment.

Two phase III studies, the first to assess the safety, tolerability, and efficacy of odanacatib, a highly selective cathepsin K inhibitor, in reducing the risk of bone metastasis in women with breast cancer, and the second to investigate the effects of odanacatib in prolonging the time to first bone metastasis in men with CRPC, have been withdrawn before enrollment.

**Src inhibitors**

Src is the prototypic member of a nonreceptor tyrosine kinase family, the Src family kinases. Src is involved in numerous critical cell functions, including cell morphology, cell growth, proliferation and differentiation, adhesion, migration, and survival. Src was found to be essential for CXCL12 activation of AKT and breast cancer cell survival. Moreover, Src activity proved to be critical for the resistance of metastatic breast cancer cells to the proapoptotic effects of TNF-related apoptosis-inducing ligand. When this gene was deleted in mice through homologous recombination, osteoclast inactivation was the only detectable phenotypic change. c-Src is activated in osteoclasts after integrin binding when the cells attach to the bone matrix to initiate bone resorption; it mediates the complex intracellular cytoskeletal reorganization. c-Src is also activated in response to the RANKL–RANK interaction after the recruitment of TRAF6 to the intracellular domain of RANK. It binds to TRAF6 and recruits several signaling proteins, including Cbl, Pyk-2, and cortactin, which mediate polarization of the cell and the formation of the actin ring and ruffled border, in a process that is, as yet, incompletely understood.

Osteoclasts that are Src-deficient may have problems in their inability to form ruffled borders and an impaired ability to produce ATP which are both required for productive bone resorption. In the context of cancer metastasis to bone, it has been demonstrated that pharmacological inhibition of Src activity can impair the growth of prostate cancer in bone. Thus, Src may be a potential therapeutic target for the treatment of metastatic bone diseases.

There are currently 6 different Src inhibitors in clinical trials [dasatinib, bosutinib (SKI-606), AZD-0530, XL-999, KX2–391, and XL-228] for the treatment of solid tumors, with several more in preclinical development. Of these, only KX2–391—a small molecule that targets the protein substrate-binding site on Src rather than its ATP-binding site—is Src specific, the rest inhibit a variety of Src family kinases along with additional tyrosine kinases. Dasatinib is currently approved for the treatment of imatinib-resistant...
chronic myelogenous leukemia and Philadelphia chromosome–positive acute lymphoblastic leukemia.

Dasatinib is the best studied Src inhibitor. Preclinical studies have shown that this agent reduces the metastatic potential and induces apoptosis in several malignancies such as pancreatic, head and neck, and lung cancers.\(^{187}\) In vitro and in vivo experiments on breast cancer cells and animal models have documented repression of Src expression and activity reduces the development of metastatic skeletal disease.\(^{180,187,188}\) Phases II and III clinical trials are active to define the value of dasatinib and other Src inhibitors (eg, bosutinib, AZD0530, XL99) in the treatment of metastatic bone disease when administered alone or in combination with zoledronate acid.\(^{15}\)

Saracatinib (AZD0530) is an orally active small molecular weight inhibitor of c-Src and BCR-Abl. Its efficacy in bone resorption has been demonstrated in 2 phase I clinical trials.\(^{189}\) Dasatinib, saracatinib, and bosutinib are currently being investigated in early clinical trials in patients with prostate or breast cancer. Results have also been reported from a phase 1/2 study of dasatinib administered in combination with docetaxel in patients with progressive CRPC. Bone markers (uNTx, BAP) decrease, a prostate-specific antigen decline, and RECIST partial response was registered.\(^{190}\)

CGP76030, a c-Src inhibitor, decreased the morbidity and lethality and also suppressed the metastasis-induced osteolysis of the mice inoculated with MDA-MB-231 breast cancer cells.\(^{188}\) c-Src inhibitors include pyrimidinylaminothiazole-based BMS-354825 (dasatinib), quinazoline-based AZD0530, quinoline-based SKI-606 (bosutinib), pyridopyrimidinone-based PD180970, pyrazolopyrimidine-based PP1, and pyrrolopyrimidine-based CGP76030.\(^{169}\)

**Alphavbeta3 integrin blocker**

The integrin alphavbeta3 mediates cell–matrix interactions.\(^{191}\) Vitaxin, a humanized monoclonal antibody that blocks human and rabbit alphavbeta3 integrins, is in clinical trials for metastatic melanoma and prostate cancer. Vitaxin decreases bone resorption by impairing osteoclast attachment, without affecting osteoclast multinucleation. Data also show that Vitaxin’s inhibitory effects on osteoclasts can be modulated by factors known to alter the conformation of alphavbeta3.\(^{192}\)

**Endothelin pathway**

The endothelins (ET) are peptides containing 21 amino acids produced by a variety of normal cells, such as endothelial cells, vascular smooth muscle cells and various epithelial tissues. Endothelin -1 (ET-1) was first identified as a potent vasoconstrictor and since found to have many actions,\(^{193}\) including regulation of blood pressure, renal sodium excretion, cardiac remodeling, and nociception.\(^{194}\) The ET family comprises four isoforms ET-1-4 (the most recently identified). The conversion to the active ET-1 form, after proteolytic cleavage of its inactive precursor, is the main regulatory step in controlling ET-1 levels within the body. Endothelins exert their effects by binding to 2 distinct G protein-coupled receptors, designed as ET A receptor (ETAR) and ET B receptor, with different affinity for the 2 receptors.

Prostate epithelial cells secrete large amounts of ET-1.\(^{185,186}\) ET-1 is secreted by a majority of prostate cancer cell lines.\(^{186}\) In men with advanced prostate cancer, plasma ET-1 concentrations are increased compared with men who have local disease or age-matched controls.\(^{187}\) In the bone microenvironment, ET-1 released from prostate bone metastases activates ETAR on osteoblasts leading to their proliferation and to an increase in bone density increase. Moreover, proliferating osteoblasts release growth factors that stimulate survival and growth of tumor cells in the bone microenvironment. Cancer cell–derived ET-1 stimulates osteoblast function via inhibition of DKK1 synthesis.\(^{194}\) ETAR antagonists reduce the progression of bone metastasis\(^{195,196}\) and decrease markers of bone turnover in men with advanced prostate cancer.\(^{200}\)

Atrasentan is an inhibitor of the ET-A receptor that has been shown to block formation of osteoblastic metastases in mice. In a placebo-controlled phase II trial in men with asymptomatic hormone refractory prostate metastatic cancer, atrasentan significantly delayed the time to disease progression compared with placebo.\(^{198}\) In a subsequent placebo-controlled phase III trial in men with metastatic prostate cancer, atrasentan (10 mg/d) did not reduce the risk of disease progression and cancer-induced bone pain or an overall survival benefit was detected.\(^{201}\) Recently, a phase 2 study to investigate the safety and efficacy of the specific ETAR antagonist ZD4054 in patients with metastatic hormone-resistant prostate cancer who were pain free or mildly symptomatic for pain was carried out. Patients were randomized into 3 groups to receive once-daily oral tablets of ZD4054 10 mg, or 15 mg, or placebo. The primary end point of time to progression was not achieved in this study, but an improvement was seen in overall survival in both active treatment arms.\(^{202}\) Zibotentan (ZD4054) is an oral specific ETA receptor antagonist and is currently under clinical evaluation through a program consisting of 3 randomized double-blind trials called ENTHUSE (ENdothermalin A USE) M0, M1, and M1c.\(^{203}\)
MISCELLANEOUS POTENTIAL FUTURE THERAPIES FOR POM

CXCR4 antagonists

Accumulating data suggests that CXCL12/CXCR4 axis participates in the development of skeletal metastases.\textsuperscript{204} Consistent with this, blockade of CXCR4 with the use of neutralizing antibodies or synthetic peptidic antagonist reduces the development of experimental lung and bone metastases from CXCR4-expressing breast or prostate cancer cells.\textsuperscript{205,206} Smith \textit{et al.}\textsuperscript{207} observed that in mice, RNA interference of CXCR4 reduced tumor burden at primary sites, and that animals transplanted with CXCR4 RNA interference tumor cells were rescued from the development of macroscopic metastases.

Daily treatment with CTCE-9908, a peptide analog of SDF-1 and competitive inhibitor of CXCR4, has been demonstrated to reduce the incidence and size of bone metastatic lesions derived from MDA-MB-231 cells or derivative bone metastatic subpopulations following injection into the left cardiac ventricle of nude mice.\textsuperscript{208,209} Plerixafor (AMD 3100), a small molecule CXCR4 antagonist, is currently being investigated in clinical trials as a hematopoietic stem and progenitor cells mobilizer and anticancer drug for the treatment of lymphoma, leukemia, and multiple myeloma. It is also notable that CXCR4 signaling may mediate morphine-induced tactile hyperalgesia.\textsuperscript{210} Thus, a combination of an opioid and a CXCR4 antagonist (eg, AMD 3100) may be of potential benefit for the treatment of painful osseous metastases in the future.

MISCELLANEOUS RECEPTORS THAT MAY CONTRIBUTE TO POM

Transient receptor potential vanilloid 1/ acid-sensing ion channel 3 receptors

Studies in both humans and animals have suggested that osteoclasts play a significant role in cancer-induced bone loss\textsuperscript{211} and contribute to the etiology of bone cancer pain.\textsuperscript{212,213} Osteoclasts are terminally differentiated, multinucleated, monocyte lineage cells that resorb bone by maintaining an extracellular microenvironment of acidic pH (4.0–5.0) at the osteoclast–mineralized bone interface.\textsuperscript{214} Thus, osteoclast-mediated bone remodeling results in robust production of extracellular protons,\textsuperscript{215} which are known to be potent activators of nociceptors.\textsuperscript{216} This raises the possibility that the acidic microenvironment produced by osteoclasts contributes significantly to bone cancer-associated pain through activation of acid-sensitive nociceptors that innervate the marrow, mineralized bone, and periosteum.\textsuperscript{217}

Studies have shown that subsets of sensory neurons express different acid-sensing ion channels.\textsuperscript{216} Two acid-sensing ion channels expressed by nociceptors are transient receptor potential vanilloid 1 (TRPV1) and acid-sensing ion channel-3.\textsuperscript{216} Both these channels are sensitized and excited by a decrease in pH in the range of 4.0–5.0, which is generated by osteoclasts.\textsuperscript{216}

Tissue acidosis may activate nociceptors that innervate the bone through multiple mechanisms,\textsuperscript{212,216} but TRPV1 has been proposed to play a major role in acid-induced activation of nociceptors. Systemic administration of a potent TRPV1 antagonist, 5-iodoresiniferatoxin, reduced bone cancer-related pain behaviors without producing any observable side effects in a dose-dependent fashion at day 14 after sarcoma injection.\textsuperscript{217} Pharmacological studies have shown that selective TRPV1 antagonists significantly decreased ongoing (JNJ-17203212, ABT-102, and SB366791) and movement-evoked (JNJ-17203212 and ABT-102) pain-related behaviors in the mouse model of bone cancer pain, without any observable behavioral side effects.\textsuperscript{218,219}

Systemic administration of the potent TRPV1 antagonist, 5-iodoresiniferatoxin, reduced bone cancer-related pain behaviors in mice without producing any observable side effects in a dose-dependent manner at day 14 after sarcoma injection.\textsuperscript{220} Furthermore, the combination of morphine and a TRPV1 antagonist, SB366791, was shown to have a potent analgesic effect on bone cancer pain, and a subanalgescic dose of SB366791 therefore potentiated the reduced analgesic effect of morphine.\textsuperscript{219}

Nerve growth factor receptors

Neurotrophic factors may potentially contribute to nociceptive process involved in painful osseous metastases. Nerve growth factor (NGF) derived from tumor and/or tumor stromal cells binding to TrkA receptors facilitate nociception in certain types of bone metastases.\textsuperscript{221}

The analgesic efficacy of a murine anti-NGF monoclonal antibody was evaluated in 2 animal models of bone cancer.\textsuperscript{222,223} These models included the primarily osteolytic mouse osteosarcoma line that expresses high levels of NGF and the primarily osteoblastic canine ACE-1 prostate, where NGF expression is undetectable.\textsuperscript{222} In both these models, it was demonstrated that administration of an anti-NGF antibody was efficacious in reducing both early and late-stage bone cancer pain-related behaviors and that this reduction in pain-related behaviors was greater than that achieved with acute administration of 10 mg/kg of morphine.
Human clinical trials evaluating the effects of a fully humanized monoclonal antibody to NGF (tanezumab) at reducing bone cancer pain in patients with advanced breast or prostate cancer will hopefully show benefit when completed.\(^{221,224}\)

Using a mouse monoclonal antibody against NGF (anti-NGF) that is highly specific for NGF revealed virtually no cross-reactivity to other neurotrophins. Jimenez-Andrade et al\(^{225}\) showed evidence that early/sustained administration of anti-NGF results in a marked reduction of sprouting by CGRP\(^{+}\) and NF200\(^{+}\) nerve fibers in the tumor-bearing bone. Using highly sensitive reverse transcription polymerase chain reaction analysis, they were not able to find detectable levels of mRNA coding for NGF in this canine prostate cancer cell line; strongly suggesting that it is not the tumor cells that are the major source of NGF but rather it is the tumor-associated inflammatory, immune, and/or stromal cells.\(^{225}\) Furthermore, the earlier that the blockade of TrkA occurs, the more effective the control of cancer pain and the tumor-induced remodeling of sensory nerve fibers. Administration of a tropomyosin receptor kinase (TrkA) inhibitor attenuates sarcoma-induced nerve sprouting, neuroma formation, and bone cancer pain.\(^{226}\)

**Purinergic receptors**

AF-353, a selective P2X3 and P2X2/3 receptor antagonist, was administered orally to rats and found to produce highly significant prevention and reversal of bone cancer pain behavior. This attenuation occurred without apparent modification of the disease because bone destruction induced by rat MRMT-1 carcinoma cells was not significantly altered by AF-353.\(^{227}\) Using in vivo electrophysiology, evidence for a central site of action was provided by dose-dependent reductions in electrical, mechanical, and thermal stimuli-evoked dorsal horn neuronal hyperexcitability after direct AF-353 administration onto the spinal cord of bone cancer animals.\(^{227}\) A peripheral site of action was also suggested by studies on the extracellular release of adenosine triphosphate from MRMT-1 carcinoma cells. Moreover, elevated phosphorylated extracellular signal-regulated kinase expression in dorsal root ganglion neurons, induced by cocultured MRMT-1 carcinoma cells, was significantly reduced in the presence of AF-353.\(^{227}\) These data suggest that blockade of P2X3 and P2X2/3 receptors on both the peripheral and central terminals of nociceptors contributes to analgesic efficacy in a model of bone cancer pain. Thus, systemic P2X3 and P2X2/3 receptor antagonists with central nervous system penetration may offer a promising therapeutic tool in treating bone cancer pain.\(^{227}\)

**Cannabinoid receptors (CB\(_2\))**

Cannabinoid receptor-2 (CB\(_2\)) agonists have been shown to act as an analgesic in acute, chronic, and neuropathic pain and do not lead to effects seen with CB1 agonists.\(^{228-231}\)

CB\(_2\) agonists not only produce antinociceptive and antiinflammatory effects but also have been shown to increase bone density.\(^{232,233}\) CB\(_2\) agonists increase the number of osteoblasts (bone forming cells) and inhibit the production of osteoclasts (bone destruction cells) resulting in an overall increase in bone integrity.\(^{232}\) CB\(_2\) knockout mice experience accelerated trabecular bone loss and cortical expansion further demonstrating the importance of the endogenous CB\(_2\) system in the mediation of skeletal maintenance.\(^{232}\) Mice that undergo an ovariectomy result in accelerated bone loss. These ovariectomized mice when treated with sustained CB\(_2\) agonist result in the suppression of osteoclastogenesis and increased osteoblast activity with an overall increase in bone integrity.\(^{232}\)

The activation of CB\(_2\) receptors on immune cells results in the attenuation of inflammatory factors including cytokines.\(^{234-236}\) CB\(_2\) agonists may also act by decreasing the activation of microglia in the central nervous system.\(^{237}\) CB\(_2\) agonist, AM1241, attenuates spontaneous pain behaviors in a murine bone cancer model. Sarcoma cells or cell medium were injected into the intramedullary space of the femur. Beginning on day 7, vehicle or AM1241 [intraperitoneal (i.p.), 3 mg/kg twice daily] was administered to animals. Flinching and guarding behaviors were observed to assess spontaneous pain in mice after surgery. The number of flinches was reduced by AM1241 (i.p.) treatment in tumor-bearing mice compared with mice treated with vehicle. AM1241 treatment attenuated guarding behavior in tumor-bearing mice compared with mice treated with vehicle.\(^{238}\)

Acute treatment with the CB2 agonist, AM1241, attenuated bone cancer–induced spontaneous and evoked pain, which was blocked by the CB2 antagonist SR144528. The CB2 agonist, AM1241, attenuated evoked pain behaviors in a murine bone cancer model. Tactile allodynia and movement-evoked pain were tested. AM1241 (i.p.) treatment blocked tactile allodynia in cancer-induced mice compared with cancer-induced mice treated with vehicle on days 10 and 14. AM1241 (i.p.) treatment significantly alleviated movement-evoked pain on day 14 in tumor-bearing mice treated with AM1241 compared with cancer-induced mice treated with vehicle.\(^{238}\) There was a significant reduction in sarcoma-induced bone loss and a reduction...
in the number of unicortical fractures as a result of the administration of the AM1241.  

CONCLUSIONS

Metastatic disease to the bone has been a crippling devastating complication of various cancers, leaving patients bedridden or wheelchair bound and victims suffering with unbearable pain. Knowledge surrounding the pathophysiology of painful osseous metastases is rapidly changing. Treatment approaches continue to be introduced into practice as they are approved. The advent of intravenous bisphosphonates has not only given clinicians another agent to reduce pain but also to reduce and/or postpone the risk of SREs. RANK-L inhibition with denosumab represents a new therapeutic approach to also prevent or delay SREs as well as reduce pain. A greater understanding of the pathophysiology of painful osseous metastases may lead to improved analgesia with minimal adverse effects by using tailor-made selective targeted therapy. It is hoped that potential future therapeutic agents for the treatment of painful osseous metastases may revolutionize current pharmacologic approaches and lead to improved patient outcomes with better quality of life.

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Painful Boney Metastases

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Painful Boney Metastases

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