

Comprehensive Review

 Painful Osseous 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 affect roughly 400,000 United States citizens annually. Carcinoma from breast, lung, and prostate cancers account for about 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 is 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 may also 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 systemic analgesics, intrathecal analgesics, glucocorticoids, radiation (external beam radiation, radiopharmaceuticals), ablative techniques (radiofrequency ablation (RFA) and cryoablation), bisphosphonates, chemotherapeutic agents, inhibitors of RANK-RANKL interaction (e.g., denosumab), hormonal therapies, interventional techniques (e.g., kyphoplasty), and surgical approaches. Although the mechanisms underlying the development of bone metastases are not completely 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.

**Key words:** Cancer pain, metastasis, osseous metastasis, bone pain, radiation therapy, radiopharmaceuticals

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**W**orld health experts estimated that in 2008 there were over 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 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 about 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 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" (SRE) (7). Not all patients with bone metastases have pain, but about 83% of patients with osseous metastases complain of pain at some point with wide variation in pattern and severity (8,9).

Payne and Janjan (10,11) 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. Treatment strategies have employed various therapies for the treatment of painful osseous metastases including bisphosphonates (12), chemotherapeutic agents such as mitoxantrone (a chemotherapeutic agent that inhibits DNA synthesis) (13), opioids, hormonal therapy, and interventional and surgical approaches (14-20). These patients may also present with concurrent nociceptive and neuropathic pain syndromes, which may be treated with interventional techniques, among others (21-62).

Metastatic bone disease is classified as osteolytic and osteoblastic; however, usually lesions lie within a spectrum of these 2 entities (Fig. 1). As denoted by their names, osteolytic metastases, which are considerably more common, are characterized by significant bone disruption due to augmented osteoclastic activity; on the contrary, osteoblastic metastases are characterized by overproduction of osseous tissue by activated osteoblasts (63).

### 1.0 PATHOPHYSIOLOGY OF BONE METASTASES

In order for bone metastases to develop, cancer cells first have to metastasize to the bone marrow

which is mainly composed of hematopoietic stem cells (HSCs) residing in 2 different biological structures known as osteoblastic and vascular niches (64). Communications between osteoblasts as well as other tumor stromal cells and HSCs are mainly driven via chemoattractive factors such as the stromal-derived factor 1 (SDF-1) on stromal cells and its receptor CXCR4 on HSCs (65).

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 due to  $\alpha v \beta_3$ . This is facilitated by cathepsin K exposing the Arg-Gly-Asp (RGD) sequence from collagen to  $\alpha v \beta_3$ . Osteoclast activation appears to contribute to osteolytic lesions/erosions and pain. c-Src kinase activity is increased in response to integrin binding as well as RANK-RANKL interaction, and increased c-Src is involved in promoting osteoclast function/activation.

The development of bone metastases is a multi-step process which 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) chemoattraction 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 (66-68).

Tumor cells achieve local bone resorption by che-

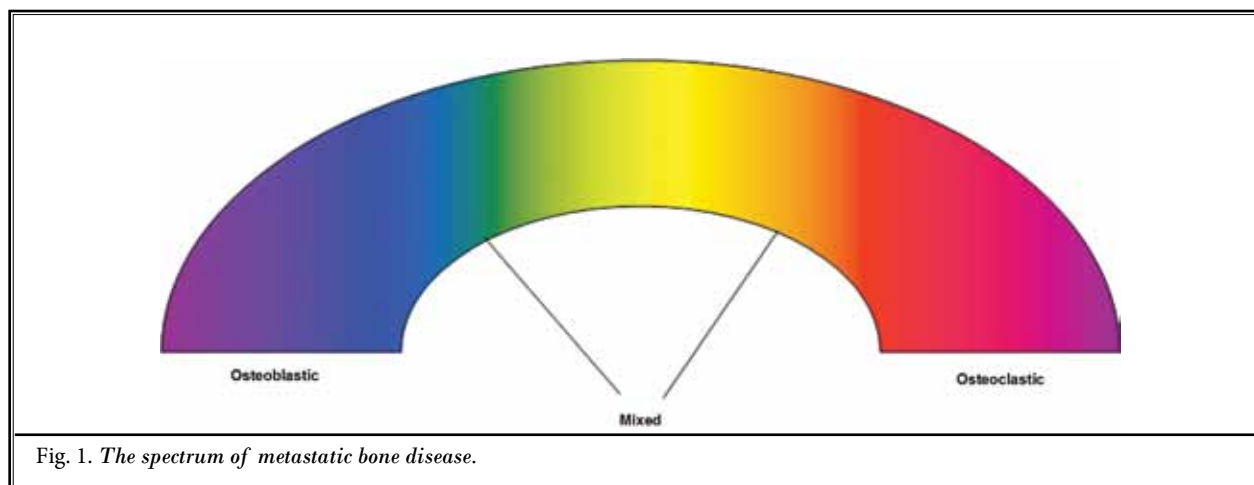


Fig. 1. The spectrum of metastatic bone disease.

motactically 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  $\kappa$ B (NF $\kappa$ B) 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 (69). The soluble glycoprotein OPG is a decoy receptor that binds to RANKL and thus inhibits RANK-RANKL interaction (68). OPG administration significantly reduces prostate cancer progression in bones because it inhibits tumor cell migration and bone resorption (70).

Secreted urokinase (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, due either to the direct protease activity of uPA or to the indirect uPA-mediated generation of plasmin and subsequent activation of matrix metalloproteinases (MMPs) (71,72).

Insulin-like growth factor (IGF-1) is locally produced in bones by osteoblasts, and its bioavailability is further potentiated by the uPA/plasmin cascade-mediated release of IGF-1 from IGF binding proteins (IGFBPs) via hydrolysis of IGFBPs. It has been shown that the increased IGF-1 production at the sites of bone metastasis is modulated by functional glucocorticoid receptors (GRs) in both prostate cancer cells and osteoblasts (72-75).

## 2.0 PATHOPHYSIOLOGY OF BONE RESORPTION

Bone metastases may lead to pain via stimulation of nociceptors by algogenic mediators (e.g., cytokines, prostaglandin E, bradykinin, serotonin, substance P). Involvement or invasion, stretching, or compression of pain-sensitive 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 intra-osseous pressures (> 50 mm Hg) (76).

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<sup>+</sup>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 bone. The podosomes are made up of integrins and cytoskeletal proteins: actin microfilaments surrounded by vinculin and talin (77).

The predominant attachment site is the vitronectin receptors (e.g.,  $\alpha$ v $\beta$ 3 integrin), which recognizes the RGD amino acid sequence in various bone matrix pro-

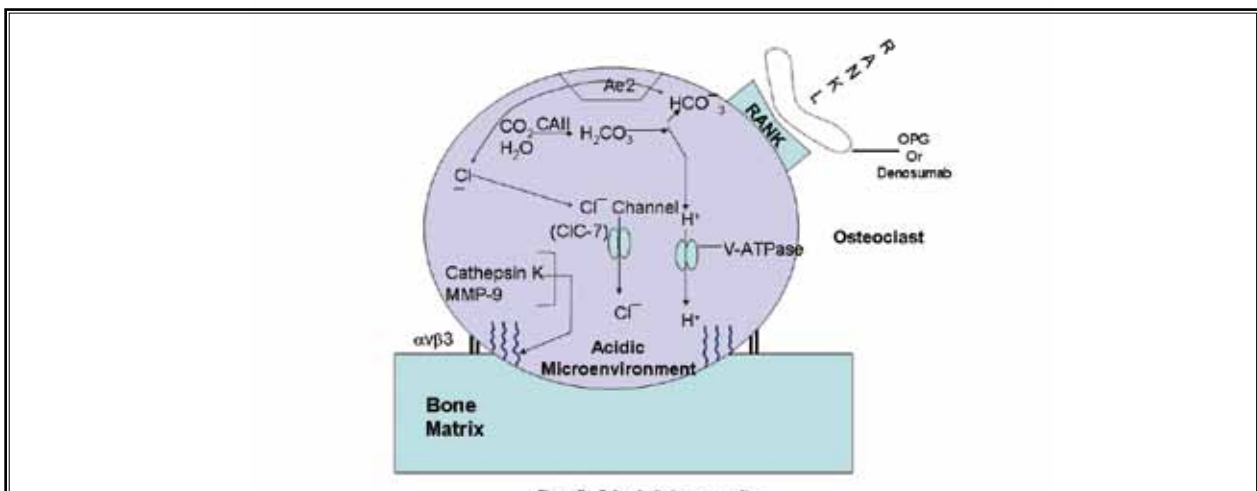


Fig. 2. Osteoclastic bone resorption.

teins (osteopontin, vitronectin, bone sialoprotein) (77). L-000845704, an  $\alpha$ v $\beta$ 3 integrin antagonist, as an antiresorptive drug (78). 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-PTPe) at its C-terminal residue Y638, supports osteoclast adhesion, and activation as well as proper structure, stability, and dynamics of podosomes (79).

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 ligand binding to the vitronectin receptor (77). 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 (77).

In order to effectively "digest" inorganic bone matrix components (e.g., hydroxyapatite), at least 2 major factors are needed: a) acid (e.g., HCl) and b) energy (e.g., ATP). The osteoclasts generate  $H^+$  and  $Cl^-$  utilizing carbonic anhydrase II (CAII) that catalyzes conversion of carbon dioxide [ $CO_2$ ] and water [ $H_2O$ ] into carbonic acid [ $H_2CO_3$ ], which in turn dissociates into hydrogen ion [ $H^+$ ] and bicarbonate [ $HCO_3^-$ ] (80,81). The  $HCO_3^-$  ions are then exchanged for  $Cl^-$  through the basolaterally located Anion Exchanger 2 (AE2) (82,83), providing the  $Cl^-$  ions required for acidification [HCl] occurring in the resorption lacuna (Fig. 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 adenosine triphosphate (ATP), containing the  $\alpha$ 3 subunit (84-87), and passive transport of chloride through the chloride channel [ClC-7], also to the bone surface (Fig. 2) (88-92). Hydrochloric acid lowers the pH to approximately 4.5, leading to dissolution of the inorganic matrix of bone (93).

Thus, involvement of vacuolar  $H^+$ -ATPase and carbonic anhydrase (CA) are crucial to "digesting" bone with subsequent creation of osteolytic lesions. c-Src may contribute to bone resorption, in part by a) preventing the inhibitory effects of calcitonin on osteoclast function and facilitating osteoclast activation, b) 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), c) facilitating podosome activities by pro-

moting a shift from stable focal adhesions with actin stress fibers to more dynamic podosome assemblies, d) 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 (94-96) (Fig. 3). The ATP produced by c-Src-induced cytochrome c oxidase activity may be utilized 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 active at low pH (97-100), and performs almost complete removal of the type I collagen fibers (101). The MMPs are also involved in the degradation of the organic matrix of the bones; however, their precise role is remains uncertain (Fig. 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 bone. Instead, they secrete paracrine factors, such as parathyroid hormone-related peptide (PTHrP) and interleukin-6 (IL-6), which directly or indirectly stimulate osteoclast differentiation and activation. In turn, bone resorption by osteoclasts releases growth factors such as transforming growth factor-beta ( $TGF\beta$ ) and insulin-like growth factor-1 (IGF-1) from the bone matrix that stimulate PTHrP production and promote tumor growth. This interaction between tumor cells and the bony microenvironment results in a vicious cycle of bone destruction and tumor growth (102). Furthermore, excessive osteoclastic bone destruction could be a factor that causes the complications of metastases (103).

This cycle involves overproduction of PTHrP by breast cancer cells that has a profound effect on tumor cell activities and survival and, when present in the bone microenvironment, results in osteoclastic bone resorption (104,105). The resorbed bone releases  $TGF\beta$ -stimulating tumor cell proliferation and consequently increased PTHrP secretion, thus continuing the vicious cycle. Furthermore, PTHrP is regulated by Gli, a Hedgehog signaling factor, and this pathway leads to pathologic consequences in a variety of human tumors (106). It has been shown that runt-related transcription factor 2 (Runx2) regulates  $TGF\beta$ -mediated activation of PTHrP

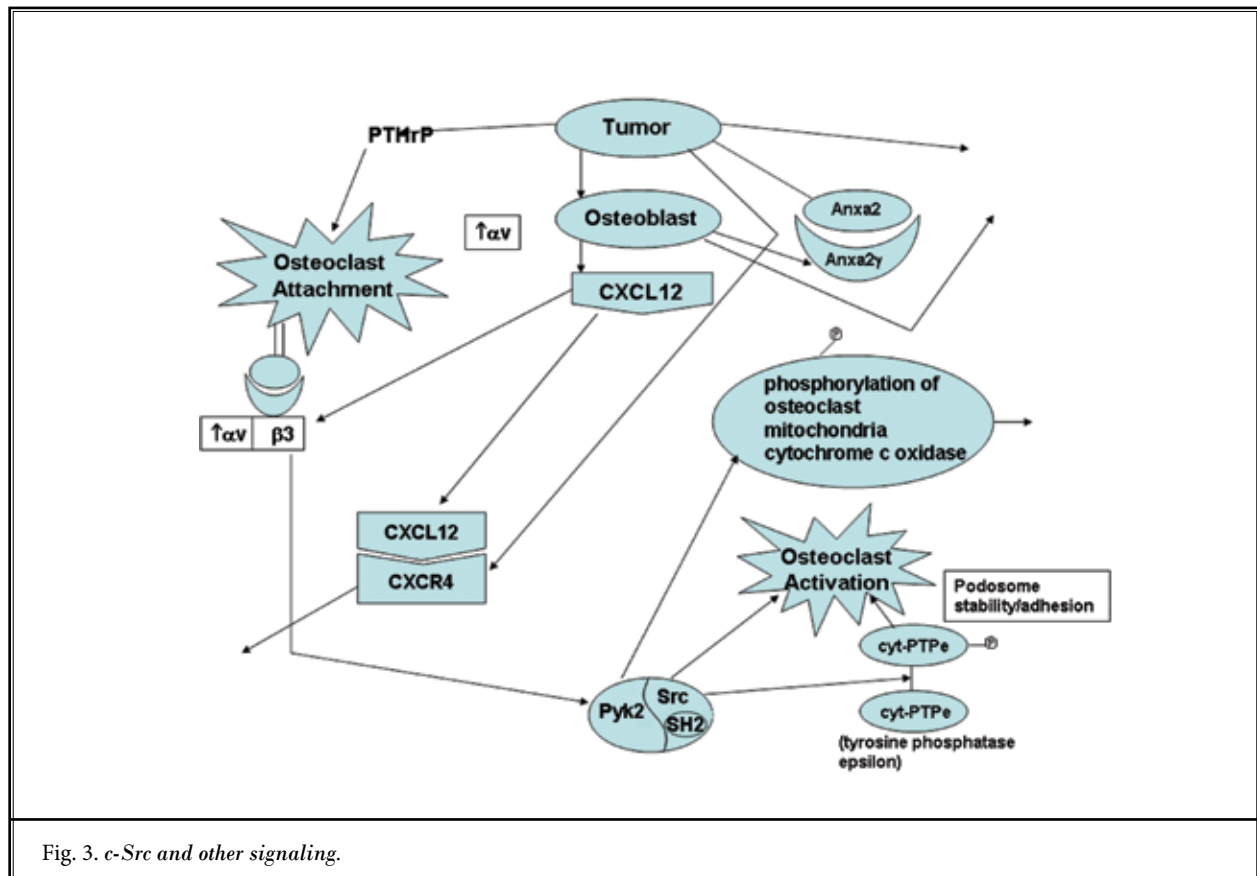


Table 1. Major Processes that may be therapeutic targets for palliation of painful osseous metastases

Target	Process	Potential Therapy
CXCR4	Communication (between tumor and hematopoietic 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)		Cathepsin K Inhibitors
RANKL-RANK interaction	Osteoclast Activation	Denosumab
Prenylation of Src		Bisphosphonates
Src		Src Inhibitors
Src	Src $\rightarrow$ ATP $\leftrightarrow$ binding to P2X3, P2X2/3 Energy $\downarrow$ Nociception	Src Inhibitors
Vacuolar H <sup>+</sup> -ATPase	Bone Resorption - Acidic Microenvironment (proton secretion) - dissolution of Inorganic Matrix	Inhibitor of vacuolar H <sup>+</sup> -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

through interaction with Hedgehog signaling molecule Gli2 (107). Runx2 binds to the Indian Hedgehog (IHH) promoter and activates its expression in cancer cells, further increasing PTHrP levels, resulting in operation of the vicious cycle in cancer cells.

Runx2, a Runx transcription factor, promotes breast and prostate tumor growth and associated osteolytic lesions in the bone microenvironment, in part through direct transcriptional activation of genes that promote bone degradation, MMP9, MMP13, and other MMPs (108,109). Moreover, (ribonucleic acid (RNA) interference treatment) with small interfering RNAs (siRNA) against Runx2 to functionally deplete Runx 2 in PC3 prostate cancer cells or MDA-MB-231 breast cancer decreases cell migration and invasion through Matrigel in vitro, and in vivo Runx2 knockdown (shRunx2) stable expression cells blocked the ability of these tumor cell lines to survive in the bone microenvironment (107,109,110).

### **3.0 PHARMACOLOGIC APPROACHES**

The standard or traditional pharmacologic approach to the treatment or palliation of painful osseous metastases (POM) follows the World Health Organization (WHO) analgesic step ladder guidelines approach to pain relief (111,112). 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 (113). By 1993 it had been translated into 22 languages (113). The WHO guidelines have been prospectively and cross-culturally validated and shown to work well clinically (113). Zech et al (114) published the largest prospective trial of WHO guidelines to date and achieved favorable pain control in 76% of 2,118 cancer patients who were treated over a 10-year interval. Analgesic agents which may play a role in the WHO guidelines approach include acetaminophen, traditional or nonselective (NS) nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, antidepressants, anticonvulsants, muscle relaxants, alpha-2 adrenergic agonists, n-methyl-d-aspartate (NMDA) receptor antagonists, and opioids/opioid-like analgesic agents.

#### **3.1 Nonsteroidal Anti-Inflammatory Drugs**

The use of traditional (nonselective [NS]) NSAIDs in cancer-induced bone pain (CIBP) has been questioned due to the lack of robust, clinical evidence. The 3 randomized trials of NSAIDs in cancer pain do not separate

out bone metastases, and 6 non-randomized trials mention bone metastases but do not record incident pain (115,116). COX-2 inhibitors may in theory be of greater therapeutic potential due to their anti-tumor/antiangiogenic properties (117,118). In an animal model of 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 (119).

Lumiracoxib (Cyclooxygenase-189) is a highly selective COX-2 inhibitor which is not Food and Drug Administration (FDA) approved in the United States. Compared with diclofenac, lumiracoxib has substantially reduced affinity for COX-1, being 300-fold less potent. The pKa 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.

#### **3.2 Opioids**

One of the major classes of agents for the pharmacologic management of POM is that of opioid analgesics. While long-acting opioids are employed 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 POM. Rapid-onset opioids FDA approved in the United States include oral transmucosal fentanyl citrate (OTFC) [Atiq], fentanyl buccal tablet (FBT) [Fentora], fentanyl buccal soluble film (FBSF) [Onsolis], and sublingual fentanyl (SLF) [Abstral]. Potential future rapid-onset opioids may include intranasal fentanyl spray (INFS) [Instanyl], fentanyl pectin nasal spray (FPNS) [Pec Fent], and fentanyl dry powder intrapulmonary inhaler [TAIFUN]. However, opioids may be overused, abused, or misused in chronic cancer and non-cancer pain (120).

#### **3.3 Anti-Epileptics**

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 (121). Stimulated by favorable effects of gabapentin in animal models demonstrated modulation of continuous and stimulus-related bone pain (121,122), and by the observation that gabapentin is reported to be useful for the treatment of neuropathic cancer pain (123), and as a synergistic adjuvant to opioid analgesics. Caraceni and colleagues (124) published

an anecdotal report describing their treatment with gabapentin of 6 consecutive patients with incident pain caused by bone metastases 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.

### 3.4 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 osteoprotegerin production (although that may only account for a small part of bisphosphonate actions) (125).

Early-generation bisphosphonates (i.e., 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 (126,127). Later generation, nitrogen-containing bisphosphonates (i.e., 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 (e.g., isoprenoid lipids) necessary for post-translational 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 (126,127). Additionally, nitrogen-containing bisphosphonates may lead to the accumulation of isopentyl pyrophosphate (IPP) which may be conjugated with adenosine monophosphate (AMP) to form an endogenous ATP analog triphosphoric acid 1-adenosin-5'-ylster 3-(3-methylbut 3-enyl) ester [Apppl] which may inhibit mitochondrial adenine nucleotide translocase (ANT) and cause osteoclast apoptosis (128). In the United States bisphosphonates include Zoledronic acid (indicated for a range of solid tumors, with osseous metastases - breast, prostate, non-small cell lung, renal, and others), Pamidronate (included for breast cancer and multiple myeloma), ibandronate (indicated for breast cancer), and Clodronate (not approved in the United States).

Multiple studies have demonstrated the efficacy of bisphosphonates in reducing skeletal complications

and pain from bone metastases (129-131). Intravenous zoledronic acid has demonstrated the broadest clinical activity (132).

Zoledronate is the most potent of the nitrogen-containing bisphosphonates, displaying superior efficacy in inhibiting FPP synthase activity, reducing bone resorption, and relieving pain when compared with other bisphosphonates, such as clodronate and pamidronate (127,133,134). Zoledronic acid is the only bisphosphonate that has statistically shown significant reductions in skeletal morbidity, including bone pain, in patients with metastatic prostate cancer (135). Fulfaro and colleagues (136) 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 (137), inhibiting cancer cell invasion (138), and limiting metastatic outgrowth in visceral tissues at extremely high doses (139). Zoledronate treatment has been associated with a decline in circulating levels of the potent pro-angiogenic molecule, vascular endothelial growth factor (VEGF), in cancer patients (140). Zoledronate-mediated reductions in VEGF 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 (141).

Saad et al (142) initiated a randomized placebo-controlled trial of 422 prostate cancer patients and demonstrated that zoledronic acid significantly reduced the rate of skeletal-related events. Similar results have been described in patients with other tumor types such as lung cancer (143). Furthermore, zoledronic acid has been demonstrated to be superior to pamidronate in reducing skeletal complications in a randomized trial of 1,130 breast cancer patients (144). Zoledronic acid can cause flu-like symptoms that are manageable with standard treatment. Renal monitoring is recommended, and dose reductions should be given according to the package information sheet for patients with renal dysfunction. Long-term use of bisphosphonates is associated with a small risk of osteonecrosis of the jaw (145).

### 3.5 Calcitonin

Intravenous salmon calcitonin (sCT) has been trialed in efforts to achieve analgesia from painful osse-

ous metastases. Although there exist anecdotal reports of minor benefit (146,147), 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 (148). In 2003, Martinez and colleagues (149) 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 (150).

#### **4.0 HORMONAL THERAPY**

Only certain types of cancers (e.g., breast cancer, prostate cancer) may respond in some fashion to hormonal therapy. Intuitively, it would seem that any hormonal therapy which achieves antineoplastic results may also possess antinociceptive qualities under certain circumstances. An example of a cancer type which may respond to hormonal therapy is prostate cancer. Androgen deprivation therapy (ADT) is achievable with surgical castration (bilateral orchiectomy) or medical castration, which may include agents such as synthetic gonadotropin releasing hormone (GnRH) agonists (e.g., leuprolide, buserelin, goserelin, histrelin, [triptorelin is in phase II trials, also a 60 month formulation triptorelin embonate is under development]), cytochrome P450 enzyme 17A1 (CYP17A1) inhibitors (inhibition of androgen synthesis) (e.g., 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 (e.g., bicalutamide, nilutamide, flutamide, and MDV 31000 – in phase III clinical trials, BMS-641988 in phase I clinical trials), inhibitors of 5 $\alpha$ -reductase (which converts testosterone to the more potent dihydrotestosterone [DHT]) (e.g., finasteride, dutasteride), as well as other agents such as GnRH blockers (e.g., 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 estrogens (e.g., diethylstilbestrol [DES]-suppress steroidogenesis by decreasing luteinizing hormone [LH]-releasing hormone secretion and indirectly affecting pituitary LH production) (151,152).

The clinical effects of flare can be limited by concomitant antiandrogen treatment (e.g., flutamide or bicalutamide) (153), which acts to inhibit the stimula-

tory 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 (154). 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 (155). However, these approaches are used infrequently in practice due to concerns about efficacy and/or side effects, which can include cardiotoxicity, gynecomastia, breast pain, and liver toxicity (155).

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 PSA suppression, without a testosterone surge or microsurges following 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 (156).

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 (157). Several novel agents targeted 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 (158). MDV3100 is an androgen-receptor antagonist that blocks androgens from binding to the androgen receptor and prevents nuclear translocation and co-activator recruitment of the ligand-receptor complex, as well as inducing tumor cell apoptosis, and has no agonist activity. Scher et al (157) recorded encouraging antitumor activity with MDV3100 in patients with CRPC.

#### **5.0 RADIOTHERAPY**

The mechanisms of radiation-induced analgesia to metastatic bone lesions remains unknown. Although there are a number of possibilities to explain this phenomenon, early pain relief with wide-field radiation therapy is so rapid that tumor cell kill cannot be a viable explanation. Pain relief, which occurs later and is persistent, certainly may be at least partially related to tumor cell kill. Also, radiation has a direct action on osteoclastic formation via effects on proliferating pro-



genitor cells, but this would also not account for early pain relief.

External beam radiotherapy (RT) rapidly inactivates radiosensitive osteoblasts. It thereby impairs osteoblastic function, including oxacillin resistant staph aureus (ORSA) release/function, which secondarily may result in impaired osteoclastic function (159). Smith (160) has proposed that radiation-induced analgesia may be at least partly due to inhibition of osteoclastic function and/or interference with purinergic signaling. Additionally, late effects include direct injury to radiosensitive proliferating osteoclast progenitor cells (159). It has been postulated that the removal of tumor cells from the bone facilitates the reparative process with osteoblasts (161).

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 (162) 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. 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 (163).

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 (164). 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 (165). These results have been confirmed in 3 metaanalyses (166-168). Wu et al (166) included 8 randomized trials (3,260 patients) in a meta-analysis, comparing 1 × 8 Gy single fraction radiotherapy with various multi-fraction regimens and found that all multi-fraction regimens were essentially equal to single fraction therapy.

Similar results have been observed in the meta-analysis of Sze et al (167), which included 3,621 patients from 12 randomized trials. The complete response rates were 34% (508/1,476) after single-fraction radiotherapy and 32% (475/1,473) after multi-fraction radiotherapy (odds ratio [OR] 1.10; 95% CI 0.94-1.30; P > 0.05).

Overall response rates were 60% (1,080/1,814) and 59% (1,060/1,807), respectively (OR 1.03; 95% CI 0.90-1.19; P < 0.05) (167-169). Chow and colleagues (168) included 5,000 patients from 16 randomized trials in their meta-analysis. The overall response rates (intention-to-treat analysis) were 58% (1,468/2,513) after single-fraction radiotherapy (mostly 1 × 8 Gy) and 59% (1,466/2,487) after multi-fraction radiotherapy (mostly 5 × 4 Gy or 10 × 3 Gy) (OR 0.99; 95% CI 0.95-1.03; P = 0.60) (168,169).

## 6.0 RADIOPHARMACEUTICAL THERAPY

Radiopharmaceuticals provide several advantages over conventional external beam radiotherapy: 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 (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

Table 2. *Treatment Guidelines*

Complete history and physical (with thorough neurological exam)
Review bone scan; check for increased uptake (hot spots) at painful areas
Complete blood counts
Perform renal studies (minimal BUN/creatinine)
Acquire informed consent
Hydrate patient
Double-check that patient is suitable candidate for therapy
Complete blood counts every other week after injection for three months or recovery to baseline counts (generally, the usual hematological response is a 20-30 percent decrease in platelet count with a nadir in about five to six weeks and recovery by 12 weeks)
Maintain a close patient follow-up post injection
Change an aspirin products (including traditional NSAIDs) to COX-2 selective inhibitors (e.g., celecoxib)
Have the patient keep a diary post injection with daily entries including evening temperature, 0-10 pain score (NRS-11), and side effects (nausea, etc.)

the patients' wishes (Table 3) (14). Multiple radiopharmaceuticals exist which may provide analgesia from painful osseous metastases, some agents have appropriate energies to be imaged as well (Table 4).

### 6.1 Strontium-89 Chloride

Strontium is a divalent cation, like calcium, and is incorporated into hydroxyapatite in the bone after intravenous injection. Sr-89-chloride (89Sr) (Metastron; GE Healthcare Global, Bucks, UK) was the first FDA-approved radiopharmaceutical for bone pain palliation (170).

89Sr (89Sr) is a calcium analog, which is preferentially deposited in osseous tissue (171). Approximately

tenfold more 89Sr is absorbed by bone metastases than by marrow (171). 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 utilized 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 (172,173). The suggested dose is 0.04 mCi/kg or 4 mCi per patient (172,173).

Pain relief usually begins within 2 weeks of treatment, with maximum benefit by 6 weeks, and lasts between 4 and 15 months (172,173). Mild thrombocytopenia or leukopenia may occur in up to 80% of patients (172,173). Platelets decline about 15%-30% below pretreatment levels and usually completely recover in 2 to 3 months, enabling repeat treatment at that time (172,173). Occasionally, recovery of platelet count to baseline may take about 6 months (172,173). In addition, 15%-20% reductions in white blood cells have also been recorded following 89Sr administration (172). A transient flushing sensation immediately after 89Sr injection has been noted and is self limited.

Kraeber-Bodéré and his group (174) used a different approach in the evaluation of 89Sr 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 89Sr. 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

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

White blood cell count < 2,500
Platelet count < 60,000 (stable)
Recent rapid fall in platelet count (even if over 60,000)
Disseminated intravascular coagulopathy
Myelosuppression chemotherapy within one month
Hemibody radiotherapy within two 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

Table 4. Characteristics of Radiopharmaceutical for the Treatment of POM

Radiopharmaceutical	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 lexidroam	1.9	0.8	103	1 mCi/kg
Rhenium – 186 Hydroxyethylidene diphosphate*	3.8	101	137	35 mCi

\* Not approved in U.S.

reduction of analgesic use ( $P = 0.018$ ), and response was significantly longer ( $P < 0.0035$ ) in patients with moderate bone involvement than in patients with extensive osseous disease (170).

A recent systematic review of the available literature published by Finlay et al (175) showed a percentage of complete responders to 89Sr 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 89Sr treatment, giving a mean overall response of 76% (170).

### 6.2 Phosphorus-32 Orthophosphate

Friedell and Storaasli (176) 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 (max 8 mm) after IV administration (177). Also, it is a pure beta emitter, and therefore cannot be imaged (177). With its high maximum energy of beta emission, it offers the greatest risk of bone marrow depression, and therefore, is hardly ever utilized for palliation of painful osseous metastases.

### 6.3 Samarium-153 Lexidronam

Samarium-153 lexidronam (153Sm-EDTMP) was originally described by William Goeckler PhD in 1984, and it was approved by the FDA on March 28, 1987, for relief of pain in patients with osteoblastic bone metastases (178,179). 153Sm-EDTMP is a stable complex of radioactive samarium-153 and ethylene diamine tetramethylene phosphonic acid (EDTMP) (180-183). Favorable features of 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 (6,180,182). The recommended dose is roughly 1.0 mCi/Kg IV administered over one minute (171-174). The onset of analgesia is about 48 hours to 7 days (180-182). Repeated doses can be administered, if necessary, at least 6 to 8 weeks after the first dose (180-182).

The group led by Sartor (184) reported the safety and efficacy of repeated doses of Sm-153 in patients

with metastatic bone pain (170). 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 proves that repeated treatment with Sm-153 is both safe and effective in patients with metastatic bone disease.

### 6.4 Rhenium-186 HEDP

Although initially developed by University of Cincinnati, Re-186 hydroxyethylidene diphosphonate (HEDP) (MDS Nordion, Ottawa, ON, Canada) is not available in the United States for clinical use. Nevertheless, it has been studied extensively and is widely used in Europe for bone pain palliation and treatment of other benign conditions (185,186).

According to a recently published European Association of Nuclear Medicine guideline, the recommended dose for treatment with Re-186 HEDP is 1.295 MBq (35 mCi) (187). Maxon et al (188) were among the first to show the beneficial effect of Re-186 in small double blind controlled trial. In this small study, a single intravenous administration of Re-186 was associated with a prompt, significant relief of osseous pain in about 80% of such patients.

The PLACORHEN study (189) was the largest double-blind placebo controlled trial performed for the efficacy evaluation of Re-186 in the treatment of metastatic prostate cancer. Of the 111 patients initially included in this trial, 79 were evaluated (43 treated, 36 placebo). The total response of the patients treated with Re-186 varied from 0% to 96% (mean, 27%). In the placebo group, the total response varied from 0% to 80% (mean, 13%,  $P < 0.05$ ). The number of patients who requested radiotherapy was higher in the placebo group (67%) than in the Re-186 (44%).

Sciuto et al (190,191) in 2 consecutive trials reported response rates of 80% and 92%, respectively. In the first study, 60 patients were evaluated with painful bone metastases from different tumor types who were treated with 1406 MBq Re-186. After treatment, the patients were followed up clinically at weekly intervals for the first month and monthly thereafter up to one-year, until death or pain relapse. Overall, 80% of individuals experienced prompt relief of pain, with 31% complete, 34% partial, and 15% minimal responses.

### 6.5 Rhenium-188 HEDP

In the past decade, Re-188 (Oak Ridge National Laboratory [ORN], Oak Ridge, TN) has gained significant clinical interest for different therapeutic applications, including bone pain palliation, particularly due to its lower cost from a tungsten-188/Re-188 generator (192). However, Re-188 HEDP has the highest energy beta emission (maximum of 2.12 MeV) among the bone-seeking agents, with the shortest mean effective biological half-life in the bone of 17 hours. Due to its high-energy beta particle, Re-188 has also the highest penetration range in the bone of 10.4 mm (170).

The efficacy of Re-188 HEDP therapy in bone pain palliation was evaluated by Liepe et al (193) in a group of 27 patients with hormone refractory prostate carcinoma. The patients were treated with doses of 2.7-3.4 GBq of Re-188 and they showed a response rate of 76% with significant improvement of the Karnofsky Performance Scale, reduction of analgesic intake and pain intensity.

Palmedo and colleagues (194) concluded that in prostate cancer patients, the maximum tolerated dose of 188Re-HEDP is 3.3 GBq if the baseline thrombocyte count is below  $200 \times 10^9/l$ . In patients with thrombocyte counts significantly above  $200 \times 10^9/l$ , a dose of 4.4 GBq might be tolerable. Thrombo and leukopenia are the most important side-effects. Pain palliation can be achieved in 60%-75% of patients receiving a dose of 2.6 GBq or more of 188Re-HEDP (194). In another study from Palmedo et al (195), the analgesia and antitumor effects of repetitive administrations of Re-188-HEDP were evaluated in patients with metastatic prostate cancer. Sixty-four patients were randomized to either a single injection of 70-90 mCi of Re-188 HEDP or 2 injections (interval, 8 weeks). They were able to demonstrate an additive effect of repetitive injections which produced an increased response rate of 92% 8 weeks later, versus a 60% response rate of the single injection. The duration of pain relief was also prolonged from 2.6 months after a single injection to 5.7 months after repeated injection. They also observed that a second injection with Re188 HEDP was sometimes effective in relieving pain, in patients who did not respond to the first injection..

The alpha-emitter 223Ra-based Alpharadin is a new radiopharmaceutical under development by Algeta ASA in collaboration with Bayer Schering Pharma AG (196). Early clinical data demonstrated that median time to PSA progression, median survival, and pain relief were superior to placebo, without dose-limiting hematological toxicity (196).

## 7.0 INTERVENTIONAL APPROACHES

Multiple interventional approaches have been described in managing chronic cancer and noncancer pain and in managing nociceptive and neuropathic pain (15-17,21-62,197-223).

### 7.1 Interventional Techniques

Watanabe and Yamakage (209) reported the successful treatment of refractory cancer pain in the lower back and lower extremities in a 60-year-old man with recurrent sigmoid cancer and metastases to the lumbar (L4-5) and sacral bones. Before the procedure he complained of severe pain despite receiving continuous intravenous infusion of morphine (7000 mg/day) with ketamine (300 mg/day) and lidocaine (700 mg/day).

### 7.2 Vertebral Ablation Procedures

Patients may be offered focal ablative therapy (radiofrequency ablation [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 one or 2 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 (197). Exclusion of patients from focal ablative therapy usually occurs when one or more of the following situations are present: a treatment requires the treatment of a portion of the lesion located within one cm of the spinal cord, major motor nerve, brain, artery of Adamkiewicz, bowel, or bladder (197), due to complications related to embolization of radicular artery (48,49,214,215).

While cryoablation may effectively treat intact or sclerotic bone, RFA energy is poorly delivered into sclerotic or otherwise intact bone (198). Cryoablation may have several other unique advantages over RFA for treatment of pain due to metastatic disease. Importantly, the zone of ablation is readily monitored with intermittent computed tomography (CT) or magnetic resonance imaging (MRI). 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 MRI (197). 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 (197,199). Furthermore, cryoblation may treat larger lesions than RFA, since the site of the ice ball generated is generally larger than the tip of the radiofrequency probe.

### 7.3 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, but also due to loss of independence, mobility, and function often with resulting isolation/loneliness (200).

#### 7.3.1 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 (201).

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 (201,214-216).

The absolute contraindications to percutaneous vertebroplasty are bleeding disorder, unstable fracture due to 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 h), 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 (201,202).

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. Polymethylmeth-

acrylate cement is then instilled under close imaging guidance until the anterior two-thirds of the vertebral body is filled and cement is equally distributed on both sides (203).

Lee and colleagues (204) 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 (205) 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 and colleagues (206) conducted a retrospective 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%. With regard to complications, no new fractures of adjacent vertebral bodies were encountered, but asymptomatic cement leakage was seen in 49% of the patients.

Chew and colleagues (207) performed a systematic review of the safety and efficacy of percutaneous vertebroplasty in malignancy. Pain reduction ranged between 47%-87%. The risk of serious complications was significant, ranging up to 2%.

#### 7.3.2 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 cement is then injected (203).

Qian and colleagues (208) 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 [SF-36] questionnaire score for function) were collected preoperatively, postoperative-

ly, and at one month, 6 months, one-year, and 2 years after treatment. Significant improvements in all of the outcome measures were observed postoperatively and throughout the duration of follow-up. The mean anterior vertebral body height variation improved from  $52.7 \pm 16.8\%$  preoperatively to  $85.3\% \pm 13.2\%$  postoperatively ( $P < 0.001$ ). Kyphotic angle improved from  $16.4^\circ \pm 4.7^\circ$  preoperatively to  $8.4 \pm 2.5^\circ$  postoperatively ( $P < 0.001$ ). The mean visual analog scale score decreased significantly from presurgery to postsurgery ( $7.4 \pm 2.1$  to  $3.8 \pm 1.6$ ;  $P < 0.001$ ), as did the Oswestry Disability Index (ODI) score ( $71.5 \pm 16.7$  to  $32.4 \pm 9.6$ ;  $P < 0.001$ ). The SF-36 scores for bodily pain, physical function, vitality, and social functioning all also showed significant improvement ( $P < 0.05$ ). Qian et al (208) 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.

#### 7.4 Intrathecal Therapies

The use of intrathecal analgesics is an important treatment consideration for many patients with chronic cancer and noncancer pain (17,22,51,219). 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 (17,22,51,219-222).

Smith and colleagues (221) performed a multicenter randomized, prospective trial evaluating intrathecal drug delivery for 202 cancer patients. Specific outcomes from the Smith et al study 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 of patients receiving comprehensive medication management, with nearly two-thirds of implantable drug delivery system (IDDS) patients, having scores in the target range of less than 4/10. The number of intrathecal drug choices are limited and should be guided by consensus guidelines (222). First-line intrathecal analgesics include morphine, sulfate, hydromorphone and ziconotide (222); however, there are other alternative agents as well (211,213,219,220,222).

Appropriate selection of patients with intractable cancer pain for chronic intrathecal analgesia therapy is paramount (17) and clear communication of the rationale for infusion is very important, as is regular education about infusion management (223).

Potential future intrathecal therapies may include cannabinoids and ginsenosides. Spinal CB1/CB2 activation via administration of an intrathecal CB1 agonist (arachidonyl-2-chloroethylamide) (224), or an intrathecal CB2 agonist (JWH015) (225), or both (WIN55,212-2) (226) reduced bone cancer-related pain behavior (224). NCTC 2472 tumor cells injection into the mice femur caused bone tumor and bone cancer pain. Intrathecal ginsenosides attenuated the bone cancer-related pain behavior. Therefore, spinal ginsenosides may be an alternative analgesic for treating bone cancer pain (227).

## 8.0 POTENTIAL FUTURE APPROACHES

### 8.1 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 a therapeutic target for the treatment of osteolytic diseases, including bone metastasis (63).

It appears 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 TNF family molecule osteoprotegerin ligand (OPGL) (228), which is expressed on activated T cells and osteoblasts, to a receptor termed receptor activator of nuclear factor  $\kappa\beta$  (NF- $\kappa\beta$ ), abbreviated RANK (228). RANK is expressed on osteoclast precursors and mature osteoclasts (69). Any treatment that impedes the OPGL-RANK interaction will impair RANK activation and therefore impair osteoclastic activity and bone resorption. Osteoprotegerin (OPG) is a soluble tumor necrosis factor 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 (Fig. 2) (228-230).

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 (231). However, due to 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 tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) mediated apoptosis in cancer cells, Amgen ceased further clinical development of AMGN-0007 (232).

Fizazi et al (233) compared the efficacy of 2 doses of denosumab (180 mg every 4 weeks or 180 mg every 12 weeks) with continued intravenous bisphosphonate-treatment (ZA 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.

The U.S. FDA 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 5,723 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 due to 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 to 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 (234).

A phase III, randomized, double-blind study that compared denosumab with zoledronate for the treat-

ment 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 as well as the overall survival were similar (235).

An example of bone biomarker use as an end point is provided by a phase II study in patients who were being treated with zoledronic acid, but whose NTx levels remained above 50 nmol/l/mmol creatinine. Denosumab was able to reduce NTx levels to below 50 nmol/l/mmol creatinine in a significantly greater proportion of patients than those who continued with zoledronic acid (233). Bone biomarkers may also be valuable in directing therapy as in the BISMARCK study, which compares standard dosing of ZOL 4mg intravenous every 3–4 weeks vs. a marker directed schedule based on updated levels of NTx (236).

Charles S. Cleeland, PhD, University of Texas M. D. Cancer Center, Houston, Texas, and colleagues (237) elsewhere examined differences between the 2 treatments in patient-reported pain interference with daily functioning using data from a phase III trial that compared denosumab with zoledronic acid in women with advanced breast cancer and bone metastases. Their findings were presented in December 2010 at the 33rd annual San Antonio Breast Cancer Symposium (SABCS).

In the trial, patients completed the 11-point Brief Pain Inventory-Short Form (BPI-SF) 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 1,018 patients treated with denosumab and 1,011 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;  $P = .09$ ). Also, time to worsening PIWA tended to be longer with denosumab than with zoledronic acid (median of 394 vs 310 days;  $P = .13$ ). 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.

## 8.2 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 partici-

pating in the process of bone turnover. This cysteine protease plays a key role in bone matrix degradation and appears to be a limiting step in osteoclastic bone resorption (238). 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 (ECM), it also exposes cryptic Arginine–glycine–aspartic acid (RGD) motifs in collagen, which are essential for osteoclast adhesion to the ECM (239).

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 (103).

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 61% when used in a prevention protocol (inhibitor administered at the same time as tumor cell inoculation) (240). Due to adverse effects in the skin, clinical development of all Cathepsin K inhibitors, except for odanacatib, have been suspended (241).

Odanacatib significantly reduced markers of bone resorption in healthy post-menopausal women (242). 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 (243).

Inhibitors of cathepsin K effectively suppress bone resorption in animal models (206). Cathepsin K inhibitor (L-006235) was shown to reduce the size of osteolytic lesions by 66% when administered 18 days after tumor cell inoculation and 61% when administered at the same time as tumor cell inoculation (240).

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 IV dose of zoledronic acid showed bone remodeling markers reduction (urinary NTx) after 4 weeks treatment (243).

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 castration-resistant prostate cancer, have been withdrawn before enrollment (244).

### 8.3 Src Inhibitors

Src is the prototypic member of a non-receptor tyrosine kinase family, the Src family kinases (245,246). Src is involved in numerous critical cell functions, including cell morphology, cell growth, proliferation and differentiation, adhesion, migration, and survival (247,248). 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 pro-apoptotic effects of TRAIL (249). When this gene was deleted in mice through homologous recombination, osteoclast inactivation was the only detectable phenotypic change (250). c-Src is activated in osteoclasts after integrin binding when the cells attach to the bone matrix to initiate bone resorption (251); it mediates the complex intracellular cytoskeletal reorganization. c-Src is also activated in response to the RANK-RANKL interaction after the recruitment of TNF receptor-associated factor 6 (TRAF6) to the intracellular domain of RANK (252). 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 (103).

Src-deficient osteoclasts result in their inability to form ruffled borders and an impaired ability to produce ATP, both of which are required for productive bone resorption (96,253,254). 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 (248,255,256). 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 (SFKs) along with additional tyrosine kinases. Dasatinib is currently approved for the treatment of imatinib-resistant chronic myelogenous leukemia and Philadelphia chro-



mosome-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 (257). 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 (250,257,258). Phase II and III clinical trials are active in order to define the value of dasatinib and other Src inhibitors (e.g., bosutinib, AZD0530, XL99) in the treatment of metastatic bone disease when administered alone or in combination with zoledronate acid (63).

Saracatinib (AZD0530) is an orally active small-molecular-weight inhibitor of c-Src and breakpoint cluster region-abelson (BCR-Abl). Its efficacy in bone resorption has been demonstrated in 2 phase I clinical trials (259). 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 I/II study of dasatinib administered in combination with docetaxel in patients with progressive CRPC. Bone markers (uNTx, BAP) decrease, a prostate-specific antigen (PSA) decline, and response evaluation criteria in solid tumors (RECIST) partial response was registered (260).

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 (258). 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 (103).

#### 8.4 WNT Pathway

Wnt are cysteine-rich, secreted glycoproteins involved in embryonic development, tissue induction, and axial polarity. Wnt ligands activate several different receptor-mediated signal transduction pathways, together with that mediated by beta-catenin, known as the canonical pathway. The Wnt pathway has been demonstrated to be a major signaling pathway in osteoblasts and activation of Wnt/ $\beta$ -catenin signaling appears to lead to increased bone mass. In the presence of Wnt ligand, Wnt binds to the receptor frizzled (Fz) and to the co-receptor LRP-5/6, leading to dishevelled protein (Dvl) activation. The binding together of these proteins into a multi-protein complex results in the inactivation of glycogen synthase kinase 3 (GSK3) via its sequestration in multivesicular bodies, and the intracellular accumulation of  $\beta$ -catenin, since GSK (being sequestered) can no longer degrade  $\beta$ -catenin like it normally does (Fig. 4).

Dickkopf homolog 1 (DKK-1) inhibits Wnt/ $\beta$ -catenin signaling and has been shown to increase RANKL/OPG ratio, thus elevated DKK1 levels may enhance osteoclastogenesis. Wnt signaling in osteoblasts upregulates

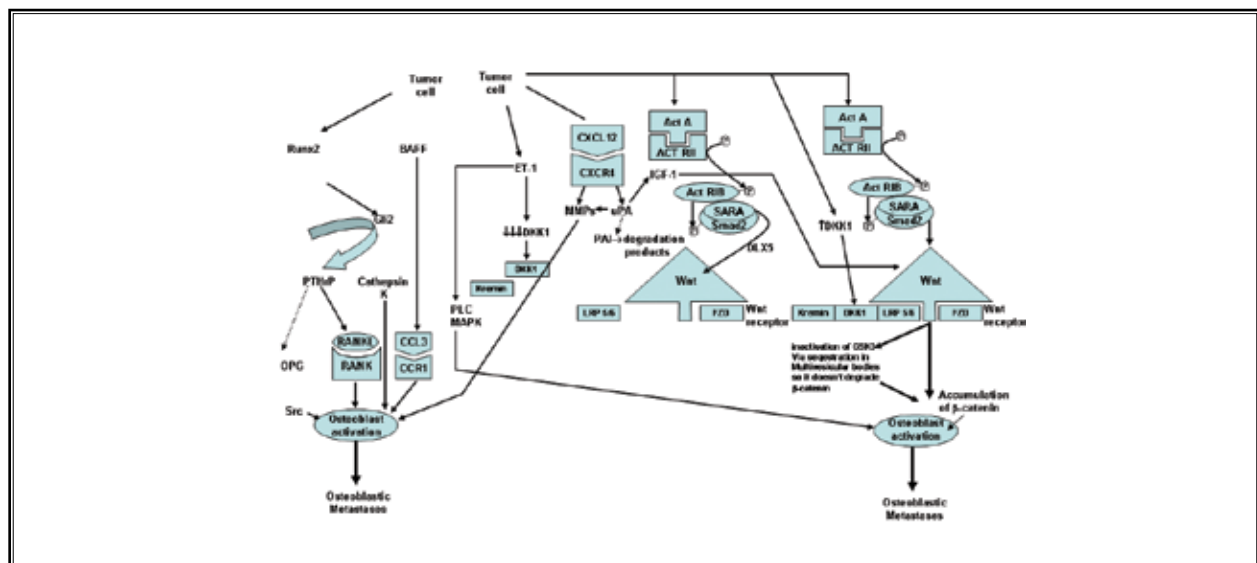


Fig. 4. Schematic of signaling contributing to bone metastases.

OPG expression and down-regulates RANKL expression (261), suggesting a mechanism by which Wnt signaling in osteoblasts indirectly regulates osteoclastogenesis. DKK1 promotes osteolytic metastases, and may facilitate the conversion of osteoblastic metastases to an osteolytic phenotype. DKK1-neutralizing antibodies restored the bone material density (BMD) of the implanted myelomatous bone in mice, increased the numbers of osteocalcin-expressing osteoblasts and reduced number of multinucleated tartrate-resistant acid phosphatase (TRAP)-expressing osteoclasts (262). BHK880, a fully human anti-DKK-1 neutralizing antibody, promotes bone formation and inhibits tumor-induced osteolytic disease in preclinical studies (263).

### 8.5 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 (264), including regulation of blood pressure, renal sodium excretion, cardiac remodeling, and nociception (265). The endothelin family comprises 4 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. ETs exert their effects by binding to 2 distinct G protein-coupled receptors, designed as endothelin A receptor (ETAR) and endothelin B receptor (ETBR), with different affinity for the 2 receptors.

Prostate epithelial cells secrete large amounts of ET-1 (266,267). ET-1 is secreted by a majority of prostate cancer cell lines (268). In men with advanced prostate cancer, plasma ET-1 concentrations are increased compared with men who have local disease or age-matched controls (268). 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 which stimulate survival and growth of tumor cells in the bone microenvironment. Cancer cell derived ET-1 stimulates osteoblast function via inhibition of DKK1 synthesis (265). ETAR antagonists reduce the progression of bone metastasis (269,270) and decrease markers of bone turnover in men with advanced prostate cancer (271).

Atrasentan is an inhibitor of the ET-A receptor that has been shown to block formation of osteoblas-

tic 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 (269). In a subsequent placebo-controlled phase III trial in men with metastatic prostate cancer, atrasentan (10 mg/day) did not reduce the risk of disease progression and cancer-induced bone pain, nor was an overall survival benefit detected (272). Recently, a Phase II 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 (273). ZD4054 is an oral, specific ETAR antagonist, and is currently under clinical evaluation through a program consisting of 3 randomized double-blind trials called ENTHUSE (ENdoTHelin A USE) M0, M1, and M1c (274).

### 8.6 Miscellaneous Potential Future Therapies for Painful Osseous Metastases

#### 8.6.1 BAFF

B cell-activating factor (BAFF) is an osteoclast-derived multiple myeloma growth factor, and its inhibition reduces tumor burden as well as lytic lesions in animal models of bone disease (275). Because the neutralizing BAFF antibody impairs multiple myeloma cell–bone marrow stromal cell interactions, the anti-osteoclastic activity observed in vivo may be mediated by reduction in multiple myeloma burden or decreased secretion of pro-osteoclast cytokines (276). Based on these data, ongoing clinical trials of BAFF neutralizing antibody (LY2127399) in combination with velcade (Millenium Takeda Oncology, Cambridge, MA) are exploring the effects on bone lesions and tumor burden.

#### 8.6.2 TGF- $\beta$

The importance of tumor-intrinsic TGF- $\beta$  signaling for promoting the ability of breast cancer cells to metastasize to bone has been demonstrated through the use of preclinical mouse models (277-279). The use of a dominant negative TGF- $\beta$  type II receptor, small-molecule inhibitors of the TGF- $\beta$  type I receptor, or ligand traps capable of neutralizing TGF- $\beta$  isoforms have all

demonstrated an ability to impair breast cancer metastasis to bone in preclinical models (277,280-282).

### 8.6.3 Activin Signaling

Activin A (Act A) is a member of the TGF- $\beta$  superfamily of growth factors which comprises a group of cytokines with similar structure but different functions (283,284). The biological effects of the activin signaling pathway are mediated by 2 transmembrane serine/threonine kinase receptors, namely type I receptor, also known as ACVR1B or ActRIB or ALK4 (activin-like kinase 4), and type II receptors ACVR2 or ActRIIA and ActRII or ACVR2 (284,285). The binding of Act A to ActRII serine kinase leads to the recruitment, phosphorylation, and subsequent activation of the type I receptor. This activation phosphorylates a subset of cytoplasmic receptor regulated Smad proteins (R-Smad). The name derives from a combination of the 2 proteins, *Caenorhabditis elegans* protein SMA and the mothers against decapentaplegic (MAD) related protein, which forms part of the complex post-receptors signal transduction system. Smad2 activation is facilitated by Smad anchor for receptor activation (SARA) which presents Smad2 to the receptor complex. Studies showed that in the presence of activated ALK4, Smad2 can function as transcriptional activator by facilitating the transcription of the canonical Wnt/ $\beta$ -catenin/Tcf4 signaling pathway (286-290). Several experimental findings, show that specific small molecule inhibitors of the Act A signaling pathway may negatively affect bone metastasis (282,291-293).

### 8.6.4 CXCR4 Antagonists

Accumulating data suggests that the CXCL12/CXCR4 axis participates in the development of skeletal metastases (294). Consistent with this, blockade of CXCR4 with the use of neutralizing antibodies or synthetic peptidic antagonists reduces the development of experimental lung and bone metastases from CXCR4-expressing breast or prostate cancer cells (295,296). Smith and co-workers (297) observed that in mice, RNA interference (RNAi) of CXCR4 reduced tumor burden at primary sites, and that animals transplanted with CXCR4 RNAi 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 (298,299). Plerixafor (AMD 3100), a small-molecule CXCR4 antagonist, is currently being investigated in clinical trials as an hydrogenated soy phosphatidyl choline (HSPC) 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 (300). Thus, a combination of an opioid and a CXCR4 antagonist (e.g., AMD 3100) may be of potential benefit for the treatment of painful osseous metastases in the future.

## 8.7 Miscellaneous Receptors That May Contribute To Painful Osseous Metastases

### 8.7.1 TRPV1/ASIC Receptors

Studies in both humans and animals have suggested that osteoclasts play a significant role in cancer-induced bone loss (301) and contribute to the etiology of bone cancer pain (302,303). 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 (304).

Thus, osteoclast-mediated bone remodeling results in robust production of extracellular protons (305), which are known to be potent activators of nociceptors (306). 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 (307).

Studies have shown that subsets of sensory neurons express different acid-sensing ion channels (306). Two acid-sensing ion channels expressed by nociceptors are transient receptor potential vanilloid 1 (TRPV1) and acid-sensing ion channel-3 (ASIC-3) (306). Both of these channels are sensitized and excited by a decrease in pH in the range of 4.0–5.0, which is generated by osteoclasts (306).

Tissue acidosis may activate nociceptors that innervate the bone through multiple mechanisms (302,306), but TRPV1 has been proposed to play a major role in acid-induced activation of nociceptors. 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 (307,308).

Systemic administration of the potent TRPV1 an-

tagonist, 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 (224). Furthermore, the combination of morphine and a TRPV1 antagonist, SB366791, was shown to have a potent analgesic effect on bone-cancer pain, and a subanalgesic dose of SB366791 therefore potentiated the reduced analgesic effect of morphine (308).

### 8.7.2 Nerve Growth Factor Receptors

Neurotrophic factors may potentially contribute to the 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 (309).

The analgesic efficacy of a murine anti-NGF monoclonal antibody was evaluated in 2 animal models of bone cancer (310,311). 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 (310). In both of 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 10mg/kg of morphine sulfate (310,311). 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 (309,312).

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 and colleagues (313) showed evidence that early/sustained administration of anti-NGF results in a marked reduction of sprouting by CGRP<sup>+</sup> and NF200<sup>+</sup> nerve fibers in the tumor-bearing bone. Using highly sensitive reverse transcription polymerase chain reaction (RT-PCR) 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 (313). Furthermore, the earlier that the blockade of tropomyosin receptor kinase (TrkA) occurs, the more effective the control of cancer

pain and the tumor-induced remodeling of sensory nerve fibers. Administration of a TrkA inhibitor attenuates sarcoma-induced nerve sprouting, neuroma formation, and bone cancer pain (314).

### 8.7.3 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, since bone destruction induced by rat MRMT-1 carcinoma cells was not significantly altered by AF-353 (315). 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 following direct AF-353 administration onto the spinal cord of bone cancer animals (315). 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 co-cultured MRMT-1 carcinoma cells, was significantly reduced in the presence of AF-353 (315). 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 (315).

## 9.0 CONCLUSION

Metastatic disease to the bone has been a crippling complication of various cancers, leaving patients bedridden or wheelchair-bound as well as suffering with unbearable pain. Knowledge surrounding the pathophysiology of POM 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 utilizing tailor-made selective targeted therapy. It is hoped that potential future therapeutic agents

for the treatment of POM may revolutionize current pharmacologic approaches and lead to improved patient outcomes with better quality of life.

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