World 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 cancer-induced pain (2-5).

Approximately half or more of patients diagnosed with cancer may experience bone pain (6). Bone is the third most common site of metastatic disease. Breast, lung, and prostate cancers are collectively responsible for about 80 percent of secondary metastatic bone disease (7). Other common types of cancer, such as thyroid, lung, and renal cell carcinomas, also display significant osteotropism. Carinomas are more likely to metastasize to bone than sarcomas. The axial skeleton is seeded more than the appendicular skeleton, particularly due to the persistence of red bone marrow in the former. The ribs, pelvis and spine are generally involved early with distal bone involvement being infrequent. Batson’s vertebral venous plexus permits malignant cells to enter the vertebral circulation without first passing through the lungs. Malignant cell survival with the development of spinal metastases may occur is common due to the sluggish blood flow in this plexus. 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).

CIBP often results in hospice or hospital admission and is associated with reduced quality of life, increased psychological distress and decreased physical and social functioning (10-12). With higher levels of disability, advanced illness and pain, comes an increased incidence of depression and anxiety (13).
CIBP does not exist as a single entity, but instead may be considered as a combination of background pain and breakthrough pain. Breakthrough pain (BTP) has been defined as ‘a transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline pain’ (14). Breakthrough pain can be divided into spontaneous pain at rest and incident pain (either volitional or non-volitional) (15,16). Breakthrough pain was present in 75% of cases of CIBP (17). Patients with breakthrough pain had greater interference on aspects of life (mood, relationships, sleep, activity, walking ability, work, enjoyment of life) than those with no breakthrough pain (P<0.01). Almost half of breakthrough pain episodes were rapid in onset (<5 min) and short in duration (<15 min). Forty-four per cent of patients with breakthrough pain had pain that was unpredictable (17). These clinical characteristics make the successful treatment of CIBP challenging. This has been supported by other studies that have shown that up to 45% of patients with CIBP report poor pain control (18,19).

Payne and Janjan recommend specialized interdisciplinary cancer center bone metastasis clinics for patients with painful osseous metastases, if available. Payne and Janjan have published an algorithm for assessment and management of these patients (20,21). Treatment strategies have employed various therapies for the treatment of painful osseous metastases including: Bisphosphonates (22), chemotherapeutic agents--mitoxantrone (a chemotherapeutic agent that inhibits DNA synthesis) (23), hormonal therapy, interventional, and surgical approaches (24). 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 (e.g., breast) and osteoblastic (e.g., prostate); however, usually lesions lie within a spectrum of these two entities (Figure 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 (25).

**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 two different biological structures known as osteoblastic and vascular niches (26). 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 (27). Communication between the tumor cells and bone marrow hematopoietic stem cells is vitally important in for the development of osseous metastases. A significant role in the interaction between cancer and bone is played by stromal-d factor 1 (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 αvβ3. This is facilitated by cathepsin K exposing the RGD sequence from collagen to αvβ3. 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 RANKL/RANK 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: (I) tumor growth, detachment of cancer cells, and invasion of the tissue stroma; (II) neoangiogenesis; (III) escape from the tissue by intravasation; (IV) survival in the circulation; (V) chemoattraction and arrest (locking and docking) in the bone marrow endothelial vessel wall; (VI) extravasation; and (VII) establishment of the metastatic microenvironment (osteoblastic metastasis) via the cross-talk between the cancer and bone cells (28-31).

Pathophysiology of bone resorption

Bone metastases may lead to pain via stimulation of nociceptors by algesic mediators [e.g., cytokines (Geis et al. demonstrated that evoked pain behavior and spinal glia activation is at least in part dependent on tumor necrosis factor receptor 1 and 2 in a mouse model of bone cancer) (32), prostaglandins, 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 mmHg) (33).

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 bone. The podosomes are made up of integrins and cytoskeletal proteins: Actin microfilaments surrounded by vinculin and talin (34).

The predominant attachment site is the vitronectin receptors (e.g., aβ3 integrin), which recognizes the RGD (Arg-Gly-Asp) amino acid sequence in various bone matrix proteins (osteopontin, vitronectin, bone sialoprotein) (34). 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 (35).

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 (34). 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 (34).

In order to effectively "digest" inorganic bone matrix components (e.g., hydroxyapatite) at least two major factors are needed: (I) acid (e.g., HCl) and (II) energy (e.g., 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⁻] (36,37). The HCO₃⁻ ions are then exchanged for Cl⁻ through the basolaterally located Anion Exchanger 2 (AE2) (38,39), 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 subunit (40-43) and passive transport of chloride through the chloride channel [CIC-7], also to the bone surface (Figure 2) (44-48). Hydrochloric acid lowers the pH to approximately 4.5, leading to dissolution of the inorganic matrix of bone (49).

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: (I) preventing the inhibitory effects of calcitonin on osteoclast function and facilitating osteoclast activation, (II) 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, (III) facilitating podosome activities by promoting a shift from stable focal adhesions with actin stress fibers to more dynamic podosome assemblies, (IV) 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) (50-52). 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 (53-56), and performs almost complete removal of the type I collagen fibers (57). The MMPs are also involved in the degradation of the organic matrix of the bones; however, their precise role is remains uncertain (Figure 2). Targeting major processes involved in painful osseous metastases may lead to novel potential future therapeutic agents (Table 1).

**Nonpharmacologic approaches to the management of POM**

Treatment strategies for painful osseous metastases include multiple nonpharmacologic approaches. These may include: physical medicine approaches, tai chi, yoga, stretching modalities, heat, cold, galvanic ultrasound, behavioral medicine approaches, cognitive behavioral therapy, mediation, hypnosis, relaxation techniques, guided imagery, and acupuncture. Bradt and colleagues performed a systematic review indicating that music interventions may have beneficial effects on anxiety, pain, mood, and QOL in people with cancer (58). Jane and colleagues conducted a randomized clinical trial was to compare the efficacy of massage therapy (MT) to a social attention control condition on pain intensity, mood status, muscle relaxation, and sleep quality in a sample (n=72) of Taiwanese cancer patients with bone metastases (59). MT was shown to have beneficial within- or between-subjects effects on pain, mood, muscle relaxation, and sleep quality.

**Pharmacologic approaches to the management of POM**

The "standard" or "traditional" pharmacologic approach to the treatment or palliation of painful osseous metastases follows the World Health Organization (WHO) analgesic stepladder guidelines approach to pain relief (60,61). 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 (62). By 1993 it has been translated into 22 languages (62). The WHO guidelines have been prospectively and cross-culturally validated and shown to work well clinically (62). 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 (63). Analgesic agents which may play a role in the WHO guidelines approach include: Non-opioid analgesics [acetaminophen, traditional or nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors], adjuvants [antidepressants, anticonvulsants, muscle relaxants, alpha-2 adrenergic agonists, n-methyl-d-aspartate (NMDA) receptor antagonists], and opioids/opioid-like analgesic agents.

**Anti-inflammatory agents**

NSAIDs appear to be particularly useful in patients with bone pain or pain related to inflammatory conditions and less useful in patients with neuropathic pain (64). However, although clinicians regard anti-inflammatory agents as important drugs for the treatment of CIBP, this has largely been based on experience rather than a strong evidence base; and the use of traditional [nonselective (NS)] NSAIDs in CIBP has been questioned due to the lack of robust, clinical evidence (65). Three randomized trials of NSAIDs in cancer pain did not separate out bone metastases, and six non-randomized trials mention bone metastases but did not record incident pain (66-73).

Eisenberg and colleagues performed a meta-analysis of the published randomized controlled trials to assess the efficacy and safety of nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of cancer pain by meta-analyses of the published randomized control trials (RCTs) (74). Twenty-five studies met inclusion criteria for analysis. Of these, 13 tested a single-dose effect, nine multiple-dose effects, and three both single- and multiple-dose effects of 16 different NSAIDs in a total of 1545 patients (74). Better pain relief was obtained from NSAIDs than placebo in three scores [summed pain intensity difference
(SPID), peak pain relief (PPAR), and total pain relief (TOPAR) based on five or six studies, and in another score peak pain intensity difference [PPID] based on eight studies. Single doses of placebo produced a 15% to 36% rate of analgesia, whereas NSAIDs resulted roughly twice as much analgesia (31% to 60%). All differences between NSAIDs and placebo comparisons were statistically significant (74). Pain was related to bone metastases in seven studies. Four studies enrolled patients with either malignant bone pain, non-bone malignant pain, or both, but results were not reported separately for bone-related and non-bone-related pain in any study. Three studies (75-77) examined the analgesic efficacy of NSAIDs specifically for malignant bone pain, but not for other types of malignant pain. Analgesic efficacy data were extractable from only two of these studies, but were not combinable because one was a single-dose trial (77) and the other a multiple-dose trial (75). The single-dose with ketoprofen study crossover reported a mean NSAID-induced PPID of 40% to 55% and SPID of 34% to 45%. The NSAID PPID in the multiple-dose study with naproxen 275 vs. 550 mg was 23% to 33% (74).

McNicol and colleagues performed a Cochrane review and evaluated forty-two trials involving 3,084 patients were included. Clinical heterogeneity of study methods and outcomes precluded meta-analyses and only supported a qualitative systematic review (78,79). They concluded that based upon limited data, NSAIDs appear to be more effective than placebo for cancer pain (7 out of 8 papers); clear evidence to support superior safety or efficacy of one NSAID over another is lacking; and trials of combinations of an NSAID with an opioid have disclosed either no difference (4 out of 14 papers), a statistically insignificant trend towards superiority (1 out of 14 papers), or at most a slight but statistically significant advantage (9 out of 14 papers), compared with either single entity. The short duration of studies undermines generalization of their findings on efficacy and safety of NSAIDs for cancer pain (78).

Cyclooxygenase (COX)-2 inhibitors may in theory be of greater therapeutic potential in well selected patients due to their anti-tumor/antiangiogenic properties (80,81); especially in patients at high risk of gastrointestinal complications and those at risk of bleeding. Studies have shown in the sarcoma model of bone cancer pain that chronic inhibition of COX-2 activity with selective COX-2 inhibitors resulted in significant attenuation of bone cancer pain behaviors [both spontaneous and movement-evoked pain] as well as many of the neurochemical changes suggestive of both peripheral and central sensitization (82). Microsomal prostaglandin E synthase-1 (mPGES-1) acts on COX-2 derived endoperoxide PGH₂ to catalyze its isomerization to PGE₂. Thus, mPGES-1 inhibition may represent a therapeutic target to treating painful osseous metastases (83). Lumiracoxib (Cyclooxygenase-189; Prexige™), is a highly selective COX-2 inhibitor which is not approved in the United States, Canada, Australia, England, and in some other countries due to hepatic related adverse events. 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

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

<table>
<thead>
<tr>
<th>Target</th>
<th>Process</th>
<th>Potential Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXCR4</td>
<td>Communication (between tumor and hematopoetic stem cell)</td>
<td>CXCR4 Antagonists</td>
</tr>
<tr>
<td>αβ3</td>
<td>Attachment [between osteoclast (αβ3) and bone/collagen (RGD)]</td>
<td>αβ3 antagonists</td>
</tr>
<tr>
<td>Cathepsin K (exposes RGD)</td>
<td>Osteoclast Activation</td>
<td>Cathepsin K Inhibitors</td>
</tr>
<tr>
<td>RANKL-RANK interaction</td>
<td>Bone Resorption-Acidic Microenvironment</td>
<td>Denosumab</td>
</tr>
<tr>
<td>Prenylation of Src</td>
<td>Prenylation of Src</td>
<td>Bisphosphonates</td>
</tr>
<tr>
<td>Src</td>
<td>Src→ATP ↔ binding to P2X3, P2X2/3</td>
<td>Src Inhibitors</td>
</tr>
<tr>
<td>Vacuolar H⁺-ATPase</td>
<td>Inhibitor of vacuolar H⁺-ATPase [V-ATPase] (e.g., bafilomycin A1) - subunit a3</td>
<td>Carbonic Anhydrase Inhibitors</td>
</tr>
<tr>
<td>Carbonic Anhydrase</td>
<td>Bone Resorption-Acidic Microenvironment (proton secretion)-dissolution of Inorganic Matrix</td>
<td>Inhibitors of CIC-7 (Chloride Channel)</td>
</tr>
<tr>
<td>CIC-7 (Chloride Channel)</td>
<td></td>
<td>Inhibitors of Ae2 (anion exchanger)</td>
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<tr>
<td>Ae2 (Anion Exchanger)</td>
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<tr>
<td>Cathepsin K</td>
<td>Bone Resorption Proteolysis-removal of collagen fibers</td>
<td>Inhibitors of Cathepsin K</td>
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<tr>
<td>MMP-9</td>
<td></td>
<td>Inhibitors of MMP-9</td>
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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.

**Steroids**

Corticosteroids are commonly used for bone-related pain management which includes dexamethasone, methylprednisolone, and prednisone. Dexamethasone is often preferred orally because of its relatively high anti-inflammatory potency and low mineralocorticoid potency; therefore, dexamethasone has a lower risk of causing salt and water retention compared to equipotent doses of other corticosteroids. The mechanism of action of corticosteroid-induced analgesia is uncertain but may be related to decreasing tumor-related edema or inhibition of prostaglandin and leukotriene synthesis.

To date, only one study specifically addressed corticosteroid use for cancer-related bone pain. This study was a 14-day, randomized, double-blind, placebo-controlled, crossover study comparing 32 mg of oral methylprednisolone (MP) (16 mg twice daily) with placebo for symptoms in terminally ill cancer patients. After the initial 14 days, patients were continued on MP for a treatment period of 20 days. Pain intensity was significantly lower after MP compared with baseline or placebo in the crossover phase; 68% of patients responded that their pain control was better with MP compared to placebo by the end of the treatment phase. Furthermore, the findings of this study suggest that MP exerts its action rapidly, and the chances of obtaining better responses after 5 days of treatment are poor (84).

**Antiepileptic drugs**

Animal models of cancer pain have demonstrated that peripheral nerve destruction can take place in both skin (85) and bone (86). Additionally, sensitization of unmyelinated primary afferent fibers and damage to small and medium sized sensory neurons may occur. Metastatic tumor cells and/or tumor stromal cells in bone appear to lead to sensory nerve injury as evidenced by changes that include: Sprouting of sensory fibers into bone (87), increased expression of activating transcription factor-3 (ATF-3) in the nucleus of sensory neurons that innervate bone, as well as up-regulation of galanin and glial fibrillary acidic protein (GFAP) with hypertrophy of satellite cells surrounding ipsilateral dorsal root ganglion (DRG) sensory neuron cell bodies and ipsilateral DRG macrophage infiltration (88).

Gabapentin and pregabalin are voltage-gated calcium channel blockers believed to exert their effects at the alpha-2-delta-1 subunit. 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 (89). In a sarcoma model chronic treatment with gabapentin did not affect tumor growth, tumor-induced bone destruction or tumor-induced neurochemical reorganization in sensory neurons or spinal cord, but did attenuate both ongoing and movement-evoked bone cancer-related pain behaviors (86). These changes suggest that there is likely a neuropathic component which exists in conjunction with nociceptive and inflammatory components in painful osseous metastases. In animal models gabapentin demonstrated modulation of continuous and stimulus-related bone pain (89,90) it has been reported to be useful for the treatment of neuropathic cancer pain (91), and as a synergistic adjuvant to opioid analgesics. Caraceni and colleagues published an anecdotal report describing their treatment of six 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 (92). Clinical trials have been underway for assessing the effects of pregabalin on attenuating chronic bone pain related to metastases (93). As far as therapeutic agents in the class of "anticonvulsants", it is conceivable that topiramate may be an antiepileptic drug which is particularly well-suited for the treatment of painful osseous metastases, since 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; GABA facilitator and may affect the NMDA receptor complex. Adequate hydration is recommended due to the potential formulation of calcium phosphate renal stones.

**Opioids**

One of the major classes of agents for the pharmacologic management of POM is that of opioid analgesics. Preclinical research suggests that there may be varying efficacy for different opioids (94), however, clinically there does not appear to be any opioid that is better than any other opioid for the treatment of painful osseous metastases. Although some opioids may provide more analgesia than other opioids for a specific individual patient, currently, "trial and error" is the only way to determine this. Opioids are considered an effective therapy for background pain in CIBP. However, their usefulness in breakthrough pain is less clear. It appears to be vitally important to match the characteristics of the opioid utilized to treat BTP; to the type of BTP experienced. Immediate release oral morphine has,
at best, an onset of action of about 30 min (95). This means that in patients with rapid-onset, short duration breakthrough pain, immediate release morphine will probably be ineffective. Furthermore, titration of opioids to doses that control episodes of breakthrough pain may result in unacceptable opioid side-effects (96). Newer, rapid-onset opioids have been developed with the aim of mirroring the temporal features of breakthrough pain.

The author suggests a "triple opioid therapy (TOT)" approach to using opioid analgesics to treat painful osseous metastases. A triple opioid therapy approach utilizes three different opioid formulations [a controlled release opioid, an immediate release opioid, and a rapid onset opioid (ROO)]. Enteral or transdermal extended release (ER) or controlled release (CR) opioids are employed for "maintenance" therapy to control the baseline or background constant pain. The patient receiving TOT then evaluates breakthrough pain (BTP) episodes; (I) if a BTP episode seems relatively predictable and gradually intensifies over a half-hour or more [Gradual Onset Breakthrough Pain (GOBTP)], then it may be treated early with an immediate release (IR) opioid formulation, however, (II) if a BTP episode is unpredictable and/or the intensity suddenly increases rapidly [Rapid Onset Breakthrough Pain (ROBTP)], then it should be treated with a rapid-onset opioid (Figure 4).

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®], sublingual fentanyl (SLF) [Abstral®], and fentanyl pectin nasal spray (FPNS) [Lazanda®] (97). Potential future rapid-onset opioids may include: Intranasal fentanyl spray (INFS) [Instanyl®] and fentanyl dry powder intrapulmonary inhaler [TAIFUN®] (97).

**Bisphosphonates**

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 (98,99). Later generation, nitrogen-containing bisphosphonates (i.e., pamidronate, ibandronate and zoledronate) inhibit osteoclasts by a different mechanism. They are internalized - but not

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Figure 4. Two different types of breakthrough pains (BTPs) and their "matching" opioid treatment.
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 (98,99). Additionally, nitrogen-contain 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-adenosine-5'-ylster 3-(3-methylbut 3-etyl) ester [ApppI] which may inhibit mitochondrial adenine nucleotide translocase (ANT) and cause osteoclast apoptosis (100). 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 (included for breast cancer and multiple myeloma), ibandronate (indicated for breast cancer), and Clodronate (not approved in U.S.).

Multiple studies have demonstrated the efficacy of bisphosphonates in reducing skeletal complications and pain from bone metastases (101-104). Intravenous zoledronic acid has demonstrated the broadest clinical activity (105). 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 when compared with other bisphosphonates, such as clodronate and pamidronate (99,106-109). Zoledronic acid is the only bisphosphonate that has statistically shown significant reductions in skeletal morbidity, including bone pain, in patients with metastatic prostate cancer (110). Fulfaro and colleagues 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 (111).

Zoledronate, in particular, has been reported to have direct antitumor properties in preclinical studies. It is capable of inducing tumor cell apoptosis (112), inhibiting cancer cell invasion (113) and limiting metastatic outgrowth in visceral tissues at extremely high doses (109). Zoledronate treatment has been associated with a decline in circulating levels of the potent pro-angiogenic molecule, VEGF, in cancer patients (114). 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 (115). Zoledronic acid distributes and bonds to osseous tissues and has a triphasic post-infusion decline process with a terminal half-life of 146 hours. Prior to therapy initiation of zoledronate, a dental evaluation and subsequent follow-up are needed in efforts to monitor for the occurrence and risk of osteonecrosis of the jaw.

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 Clcr of <30 mL/min and caution should be utilized when using coledronate in patients with other nephrotoxic agents. Dose reductions should be followed according to the package information sheet for patients with renal dysfunction.

**Hormonal approaches to the management of POM**

Modulation of various hormonal pathways may be useful in the therapeutic strategies to combat POM in certain types of cancers.

**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.

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 (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 (117). These results have been confirmed in three meta-analyses (118-120). Wu et al. (118) included eight 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. Dennis and colleagues found that patients suffering from painful bone metastases with an estimated survival of 3 months should still be considered for palliative radiotherapy (119).

**Radiopharmaceuticals**

Radiopharmaceuticals such as *Strontium-89 chloride* and
Samarium-153 lexidronam provide several advantages over conventional external beam radiotherapy: (I) they can be administered intravenously, (II) they can treat multiple, diffuse sites with mild bone marrow depression, and (III) they cause fewer adverse side-effects such as nausea, vomiting, diarrhea, and tissue damage (24).

Figuls and colleagues 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): Four (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 to 3.35; Number needed to treat to benefit (NNT)=5] and complete/partial relief (RR 1.72, 95% CI 1.13 to 2.63; NNT=4) in the short and medium term (eight studies, 499 participants) (120).

Interventional approaches to the management of POM

Ablative procedures

Patients with "relatively soft" osteolytic or mixed osteolytic/osteoblastic lesions may be amenable to focal ablative therapy [radiofrequency ablation (RFA) (121) or cryoablation] for focal painful metastatic sites.

While cryoblation may effectively treat intact or sclerotic bone, RFA energy is poorly delivered into sclerotic or otherwise intact bone (122). An advantage of cryoablation, is that the zone of ablation is readily monitored with intermittent CT or 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.

Vertebral augmentation procedures

Vertebral augmentation procedures such as percutaneous vertebroplasty and percutaneous kyphoplasty may 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 (123).

Intrathecal therapies for POM

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 (124).

First-line intrathecal analgesics include morphine, sulfate, hydromorphone and ziconotide (125), however, there are other alternative agents as well (Figure 5) (124-126).

Potential 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 (25).

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) (127), which is expressed on activated T cells and osteoblasts, to a receptor termed receptor activator of nuclear factor κB (NF-κB), abbreviated RANK (127). RANK is expressed on osteoclast precursors and mature osteoclasts (128). 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 (Figure 2) (127,129,130).

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 (131). However, due to the superior efficacy of their newer agent, denosumab (AMG-162) - a fully human monoclonal antibody that specifically neutralizes RANKL - thereby inhibiting bone resorption, and concerns regarding deleterious OPG-mediated protection from TRAIL mediated apoptosis in cancer cells, Amgen ceased further clinical development of AMGN-0007 (132).
Smith. Painful boney metastases

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=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.

Cannabinoid receptors (CB₂)

Cannabinoid Receptor-2 (CB₂) 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 (134-137). CB₂ agonists not only produce antinociceptive and anti-inflammatory effects, but also have been shown to increase bone density (138,139). CB₂ 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 (138). CB₂ knockout mice experience accelerated trabecular bone loss and cortical expansion further demonstrating the importance of the endogenous CB₂ system in the mediation of skeletal maintenance (138).

The CB₂ agonist, AM1241, attenuates spontaneous pain
behaviors in a murine bone cancer model (140). 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 to cancer-induced mice treated with vehicle on days 10 and 14. AM1241 (i.p) treatment significantly alleviate movement-evoked pain on day 14 in tumor-bearing mice treated with AM1241 when compared to cancer induced mice treated with vehicle (140).

**S-NACH**

Heparin is an unbranched, acidic glycosaminoglycan rich in N- and O-sulfate groups that is synthesized by mast cells as a component of high molecular weight proteoglycans. Heparin molecules are composed of alternating residues of D-glucosamine (or N-acetyl-glucosamine) and uronic acid (L-iduronic or D-glucuronic acid) (141). Heparin acts as an anticoagulant by accelerating the inhibition of thrombin and other coagulation enzymes by the circulating protease inhibitor, antithrombin (also called antithrombin III or AT-III) (142). However, a modified heparin S-NACH (sulfated non-anticoagulant heparin) which is devoid of AT binding and inhibition of AT-dependent coagulation factor (e.g., factor Xa and IIa) can be utilized in high doses without fear of bleeding or hemorrhagic adverse effects.

Mounting evidence indicates that P-selectin plays a crucial role during hematogenous metastasis, and P-selectin has been shown to bind to several human cancers and human cancer-derived cell lines, such as colon cancer, lung cancer, breast cancer, malignant melanoma, gastric cancer (143,144). P-selectin plays roles mainly in the initial process of tumor cell adhesion to platelets (145,146). Therefore, it is conceivable that blocking P-selectin on platelets with antagonists can effectively inhibit the formation of tumor cell-platelet emboli complexes and successfully prevent hematogenous metastasis. Several studies have demonstrated that heparin and heparan sulfate were ligands for P-selectin and could block its binding to carbohydrate ligands (147). Heparin and heparin-like oligosaccharides can inhibit P-selectin binding to SLex-related compounds (148). Inhibition of P-selectin binding results in inhibition of the inflammatory response and may attenuate tumor metastasis (147,149). Li and colleagues have suggested that the critical antimetastatic effects by heparin are mediated primarily via interference with P-selectin mediated binding (150,151).

All three selectins can bind sialylated, fucosylated, or in some cases, sulfated glycans on glycoproteins, glycolipids, and proteoglycans. The tetrasaccharides sLex and sLea have been identified as the minimal ligands for all three types of selectins.

Each of the selectins can bind to sialyl-Lewis x (sLe^x), a sialylated and fucosylated tetrasaccharide found as a terminal structure of sugar chains on glycoproteins and glycolipids expressed by a variety of cell types, including neutrophils, monocytes, and colon cancer cells (152-156).

Intravenously administered heparin tetrasaccharides diminished influx of neutrophils into the peritoneal cavities of thioglycollate-treated mice, and demonstrated anti-inflammatory activity in vivo (149).

Vik and colleagues showed that both unfractionated heparin (UFH) and high-dose LMWH (dalteparin) increase plasma osteoprotegerin (OPG) levels likely by mobilizing and attracting OPG into the vascular compartment (157).

Ariyoshi and colleagues investigated the effects of Glycosaminoglycans (GAGs) on mouse monocytic cell line in regard to their differentiation, proliferation, and function in vitro. RAW 264.7 cells were cultured with receptor activator of NF-kappaB ligand (RANKL) and various GAGs (158). Heparin suppressed TRAP-positive multinucleated cell formation and TRAP activity induced by RANKL, whereas the other GAGs showed no effects on osteoclast differentiation. Heparin also inhibited the formation of resorption pits, while the others did not. Heparin reduced the level of c-Src protein in RAW 264.7 cells stimulated with RANKL. Heparin and RANKL were subjected by HiTrap heparin column chromatography and each fraction was collected. Western blotting analysis revealed the expression of RANKL in the fraction bound to heparin. The binding of RANKL and heparin was confirmed by quartz-crystal microbalance. These results indicate that the inhibitory effect of heparin toward osteoclastogenesis induced by RANKL is due to the binding of heparin to RANKL (158). This RANKL-Heparin binding appears to interfere with osteoclast formation and function.

Data revealed that heparin inhibited osteoclastogenesis in three animal models, which was confirmed by a decrease in mRna expression of osteoclastic markers and by an inhibition of the bone resorption capacity. Baud’huin and colleagues also demonstrated in RAW 264.7 cells that other families of GAGs different from heparin inhibited RANKL-induced osteoclastogenesis, and that this inhibition was dependent on the length and the level of sulfation of GAGs. They found that heparin did not bind to RANKL and did not modulate RANKL signaling. Heparin acted at 2 distinct steps of osteoclastogenesis from human CD14(+) cells: First, heparin strongly decreased...
the adherence of osteoclast precursors, and secondly inhibited osteoclasts to spread and to be active. Furthermore, the second action of heparin was reversible as the removal of heparin at the end of the culture time allowed the condensed cells to spread out and showed the formation of morphological active osteoclasts (159).

Yee and colleagues treated C57BL/6 mice were treated with increasing doses of unfractionated heparin (15, 20, or 25 units/mouse) 30 min prior to the left ventricular injection of GFP-transfected B16F10 melanoma cells (160). Heparin's effect on tumor burden and bone strength was then quantified 14 days later by bone histomorphometry and biomechanical testing, respectively. Based on histomorphometric analysis of the femurs, injection of GFP transfected melanoma cells resulted in a 37% decrease in cancellous bone volume and a 68% increase in osteoclast surface. This was associated with a 13% reduction in bone strength as measured by biomechanical testing. However, when the mice were first pre-treated with 25 units of heparin, tumor burden was decreased by 73% and tumor cell-dependent decreases in both cancellous bone volume and bone strength were prevented (160). Yee et al. concluded that heparin inhibitors tumor cells to metastasize to bone and that as such, prevents tumor cell-induced decreases in bone strength (160).

Heparin may also attenuate the targeting of tumor cells to bone. Bone is highly vascularized, and heparin may prevent tumor cell binding to the surface of sinusoidal endothelium. Thus, many tumor cells express sialyl Lewis x on their surface. Sialyl Lewis x is the ligand for P-selectin and is expressed on the surface of activated endothelial cells. Heparin blocks P-selectin interactions with its ligand and this may prevent tumor cell-endothelial cell interactions (151,161-164). Without P-selectin binding, tumor cell adhesion to endothelium via other molecules such as integrins is either delayed or does not occur. S-NACH may combat painful osseous metastases via multiple mechanisms (Table 2).

**Potential future therapeutic agents**

Additionally, it is conceivable that potential future therapeutic agents may include nerve growth factor (NGF) inhibitors, inhibitors of cathepsin K, Src inhibitors, inhibitors of MMP-9 αβ3 antagonists, CXCR4 antagonists, endothelin-A receptor antagonists (e.g., atrasentan) (165), and tyrosine kinase inhibitors [e.g., cabozantinb (XL184)].

**Conclusions**

Metastatic disease to the bone has been a crippling devastating complication of various cancers, leaving patients bedridden or wheelchair-bound and victims of 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 “skeletal-related events”. RANK-L inhibition with denosumab represents a new therapeutic approach to also prevent or delay “skeletal-related events” 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 painful osseous metastases may revolutionize current pharmacologic approaches and lead to improved patient outcomes with better quality of life.

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71. Staquet MJ. A double-blind study with placebo control of intramuscular


