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Volume XVII, Issue 2 June 2009



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# Bone Cancer Pain

## Clinical Bone Cancer Pain

It is estimated that 8 million people from around the globe will die from cancer in 2009. While pain can occur at any point during the course of the disease, in general the more advanced the cancer, the more likely it is that the patient will experience significant pain. Although bone is not a vital organ, many common tumors (of the breast, prostate, thyroid, kidney, and lung) have a strong predilection to metastasize to multiple bones at the same time.[1,2] Tumor growth in bone results in pain, hypercalcemia, anemia, increased susceptibility to infection, skeletal fractures, compression of the spinal cord, spinal instability, and decreased mobility, all of which compromise the patient's functional status, quality of life, and survival.[1,3] Once tumor cells have metastasized to the skeleton, the "ongoing" tumor-induced bone pain is usually described as dull in character, constant in presentation, and gradually increasing in intensity with time.[3] Adherence to the World Health Organization analgesic ladder, along with adjuvant therapies such as bisphosphonates, corticosteroids, radiotherapy, and radionucleotides, can frequently control ongoing bone cancer pain, although both opioids and nonsteroidal anti-inflammatory drugs have significant dose-limiting side effects.

*Although bone is not a vital organ, many common tumors metastasize to multiple bones at the same time*

As tumor growth and tumor-induced bone remodeling progress, severe "incident pain" frequently occurs.[3] This incident pain is also known as "breakthrough pain" as the pain "breaks through" the analgesic regime that is controlling the ongoing pain. Incident pain is defined as an intermittent episode of extreme pain that occurs spontaneously (where there is no obvious precipitating event) or more commonly is induced by normally non-noxious movement[4] or mechanical loading of the tumor-bearing bone(s). Major problems with incident pain in bone cancer are that it is usually more severe than ongoing pain, it appears suddenly (within seconds to minutes), it can occur multiple times each day, and it is frequently difficult to predict.[4] With the therapies that are currently available, and with its rapidity of onset and severity, incident pain remains one of the most challenging of cancer pains to control[4] and can be highly debilitating to the patient's functional status and quality of life.[2,3,4]

## Preclinical Models of Bone Cancer Pain

Given the enormous consequences in terms of suffering that bone cancer pain can cause, it is surprising that the first animal model of bone cancer pain was developed only a decade ago.[5] Previously, two in vivo mouse models were commonly used to study tumor-induced bone destruction. In the first model, tumor cells are injected into the left ventricle of the heart and then spread to multiple sites, including the bone marrow, where they grow and induce remodeling of the

*Supported by a grant from Endo Pharmaceuticals, Inc., USA*

surrounding bone.[6,7] While this model replicates the observation that most tumor cells metastasize to multiple sites, including bone, a major problem with this model is the variability among individual animals in the sites, size, and extent of the metastasis. Since the tumors frequently metastasize to vital organs such as the lung or liver, the general health of the animal is also variable, making behavioral assessment difficult. Additionally, because the tumors frequently metastasize to bone in the vertebral column, tumor growth in the vertebrae can result in collapse of the vertebral column and compression of the spinal cord, with resultant spinal dysfunction and paralysis. Given these problems, the development of an animal model of bone cancer pain using intracardiac injection has proven difficult.

The second major model used to study tumor-induced bone destruction involves the direct injection of osteolytic sarcoma cells into the intramedullary space of the mouse tibia or femur. Previously, the major problem with this model was that the injection site could not be plugged using conventional sealing agents (as it is a wet, bony surface), and so the tumor cells rapidly escaped and avidly grew in nearby skin and joints. This rapid growth of tumor cells usually resulted in large extraskeletal tumor masses that not only interfered with behavioral analysis but also destroyed nerves passing though these sites, thereby generating a neuropathic pain state. A major advance was to plug the injection hole with a dental amalgam, which, by tightly binding and sealing the injection hole, confines tumor cells to the marrow space of the bone and prevents tumor invasion into surrounding soft tissue.[8]

*Incident pain remains one of the most challenging of cancer pains to fully control*

The first cell type that was used extensively in this model was mouse osteosarcoma tumor cells that were injected and confined to the intramedullary space of the mouse femur.[5] These tumor cells grow in a highly reproducible fashion and, as they proliferate, replace the hemapoietic cells that normally populate the bone marrow.[5,8] Eventually, the entire marrow space is filled with tumor cells and tumor-associated inflammatory/immune cells.[5,8] In terms of bone remodeling, injection of osteosarcoma cells to the femur induces a dramatic proliferation and hypertrophy of osteoclasts at the tumor-bone interface as well as significant bone destruction in both the proximal and distal heads of the femur.[8] In this model, ongoing pain and movement-evoked pain-related behaviors increase in severity with time and are correlated with tumor growth and progressive tumor-induced bone destruction,[5,8] which mirrors what occurs in patients with primary or metastatic bone cancer.

While sarcoma cells were the first tumor cells used in this model, other animal and human tumor cells, including cells from prostate, breast, melanoma, colon, and lung tumors, have now been used in the closed femur model of bone cancer pain.[9] Several studies have suggested that analgesics can not only reduce cancer pain but also influence disease progression,[10] and thus this model is useful as it allows simultaneous assessment of tumor-induced pain behaviors, tumor growth within the bone, and tumor-induced bone remodeling.

## Tumor- and Osteoclast-Induced Acidosis and Bone Cancer Pain

Reports from both animal studies and humans with bone cancer pain have suggested that osteoclasts (the cells that break down bone) play a significant role in cancer-induced bone loss[11] and that osteoclasts contribute to the etiology of bone cancer pain.[10,12] 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.[13] Tumor-induced release of protons may be particularly important in the generation of bone cancer pain (Fig. 1). Both osteolytic (bone-destroying) and osteoblastic (bone-forming) cancers are characterized by osteoclast proliferation and hypertrophy.[8,14,15]

*Osteoclasts play a significant role in bone cancer pain and cancer-induced bone loss*

Bisphosphonates are a class of antiresorptive compounds that are pyrophosphate analogues with a high affinity for calcium ions, causing them to rapidly and avidly bind to the mineralized matrix of bone.[14] As osteoclasts resorb bone, they use endocytosis to clear the bone breakdown products from the osteoclast-bone interface (including the bisphosphonate that is bound to the mineralized bone). Bisphosphonates, once taken up by the osteoclasts, induce loss of function and ultimately apoptosis of the osteoclasts by impairing either the synthesis of adenosine triphosphate or cholesterol, both of which are necessary for osteoclast function and survival.[14]

Animal and clinical studies of bone cancer have reported that the antiresorptive effects of bisphosphonate therapy simultaneously reduce bone cancer pain, tumor-induced bone destruction, and tumor growth within the bone.[10,12,16] Recent data also suggest that in addition to the antitumor effects that they produce by inhibiting the breakdown of mineralized bone, bisphosphonates may also have antitumor effects on tumor cells growing in soft tissues.[16] This systemic tumoricidal effect of bisphosphonates has been hypothesized to occur by reducing the circulating levels of vascular endothelial growth factor, which is an essential component of tumor angiogenesis.[16] Currently, clinical studies are being performed to determine the effect that bisphosphonates have on bone pain, tumor growth, and tumor metastasis in bone cancer.[17–24]

It should be stressed that while they are approved and are frequently used to reduce tumor-induced bone destruction and bone cancer pain, bisphosphonates do have unwanted side effects (including induction of arthralgias and osteonecrosis of the jaw),[14] and it has yet to be definitively shown that they increase the survival of patients with bone cancer. For this reason, other therapies targeting osteoclasts are already in mid- to late-stage clinical trials and hold significant promise for alleviating bone cancer pain and tumor-induced bone remodeling. One line of therapies attempts to block the binding of receptor activator for nuclear factor κB ligand (RANKL), which is an essential regulator of osteoclasts.[11] Studies in mice have shown that blockade of RANKL attenuates sarcoma-induced bone pain, bone remodeling, and tumor growth within the bone.[8] Recent clinical studies have shown that in humans with multiple myeloma or breast cancer metastasis

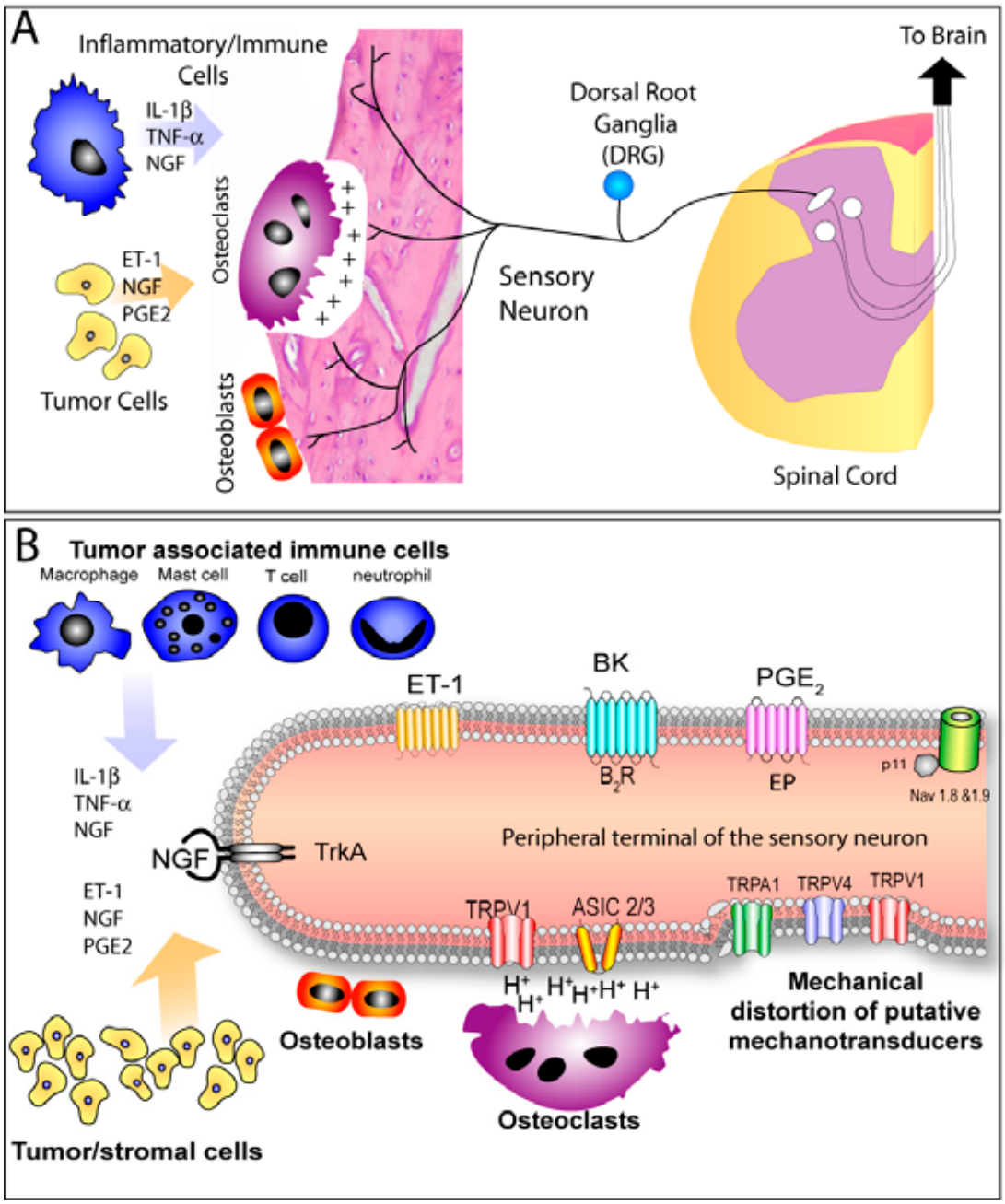


**Fig. 1.** Schematic showing factors in (A) bone and (B) receptors/channels expressed by nociceptors that innervate the skeleton that drive bone cancer pain. (A) A variety of cells, including tumor cells and stromal cells (including inflammatory/immune cells, osteoclasts, and osteoblasts) drive bone cancer pain. Nociceptors that innervate the bone use several different types of receptors to detect and transmit noxious stimuli that are produced by cancer cells (yellow), tumor-associated immune cells (blue), or other aspects of the tumor microenvironment. (B) Multiple factors may contribute to the pain associated with cancer. The transient receptor potential vanilloid receptor-1 (TRPV1) and acid-sensing ion channels (ASICs) detect extracellular protons produced by tumor-induced tissue damage or abnormal osteoclast-mediated bone resorption. Tumor cells and associated inflammatory (immune) cells produce a variety of chemical mediators including prostaglandins ($PGE_2$), nerve growth factor (NGF), endothelins (ET-1), and bradykinin (BK). Several of these proinflammatory mediators have receptors on peripheral terminals and can directly activate or sensitize nociceptors. It is suggested that movement-evoked breakthrough pain in cancer patients is partially due to the tumor-induced loss of the mechanical strength and stability of the tumor-bearing bone so that normally innocuous mechanical stress can now produce distortion of the putative mechanotransducers (TRPV1, TRPV4, and TRPA1) that innervate the bone.

to bone, denosumab (a fully humanized monoclonal antibody that inhibits RANKL) markedly reduces tumor-induced bone resorption and skeletal-related events (including fracture and pain).[25] Currently, clinical trials are underway for assessing denosumab's effects on attenuating cancer-induced bone loss in breast and prostate cancers,[26,27] its effects on skeletal-related events (pain, fracture) due to the spread of cancer to the bone in multiple myeloma and multiple solid tumors, and its potential to delay bone metastases in prostate cancer.[28]

The finding that sensory neurons can be directly excited by protons originating from cells such as osteoclasts in bone has generated clinical interest in pain research. Studies have shown that subsets of sensory neurons express different acid-sensing ion channels.[29] Two acid-sensing ion channels expressed by nociceptors are the transient receptor potential vanilloid 1 (TRPV1) and the acid-sensing ion channel-3 (ASIC-3).[29] Both of these channels are sensitized and excited by a decrease in pH[29] (Fig 1). The tumor stroma[30] and areas of the tumor that are necrotic typically exhibit lower extracellular pH than surrounding normal tissues. As inflammatory and immune cells invade the tumor stroma, these cells also release protons that generate a local acidosis.[10,31]

TRPV1 is expressed by a subset of sensory neuron fibers that innervate the mouse femur (Fig 1). An in vivo model of bone cancer pain revealed that acute or chronic administration of a TRPV1 antagonist or disruption of the TRPV1 gene results in a significant attenuation of both ongoing and movement-evoked nocifensive behaviors.[31] In addition, previous studies have also shown that in a sarcoma model of bone cancer pain, administration of a TRPV1 antagonist retains its efficacy at early, middle, and late stages of tumor growth.[31] The ability of a TRPV1 antagonist to maintain its analgesic potency with disease progression is probably influenced by the fact that sensory nerve fibers innervating the tumor-bearing mouse femur maintain their expression of TRPV1 even as tumor growth and tumor-induced bone destruction progress. These results suggest that the TRPV1 channel plays a role in the integration of nociceptive signaling in bone cancer pain and that antagonists of TRPV1 may be effective in attenuating difficult-to-treat mixed chronic pain states, such as that encountered in patients with bone cancer pain.

*Therapies targeting acid-induced activation of sensory neurons may attenuate difficult-to-treat mixed chronic pain states*

While the above discussion has focused on osteoclast-mediated acidosis as a mechanism that drives bone cancer pain, both osteolytic and osteoblastic tumors induce a loss of the mechanical strength and stability of the tumor-bearing bone so that normally innocuous mechanical stress can now produce distortion of the mechanosensitive sensory nerve fibers that innervate the bone. Previous results have shown that the pain associated with a fracture is significantly attenuated if the bone is stabilized and returned to its normal orientation.[32] Both bisphosphonates and molecules that sequester RANKL reduce the rate of tumor-induced bone remodeling and preserve the mechanical strength of bone. Preservation of the mechanical strength of bone should reduce movement-induced incident pain, which is probably driven in part by activation of normally silent mechanosensitive nociceptors that innervate the bone.

## Tumor-Derived Products in Generation of Bone Cancer Pain

In most cancers, the tumor mass is composed of tumor cells as well as tumor stromal cells including macrophages, neutrophils, T-lymphocytes, fibroblasts, and endothelial cells (Fig. 1). Tumor cells and tumor stromal cells secrete a variety of factors that sensitize or directly excite primary afferent neurons, such as prostaglandins, bradykinin, endothelins, tumor necrosis factor-α, interleukins-1 and -6, epidermal growth factor, transforming growth factor-β, platelet-derived growth factor, and nerve growth factor.[10,33] Receptors for many of these factors are expressed by primary sensory afferent neurons and present attractive targets for analgesics targeting bone cancer pain.[10]

One tumor/stromal cell product that is of significant interest in the etiology of bone cancer pain is nerve growth factor (NGF). Previous studies have shown that NGF can directly activate sensory neurons that express the TrkA receptor and that it can modulate the expression and function of a wide variety of molecules and proteins expressed by sensory neurons that express the TrkA or p75 receptor.[34] Some of these molecules and proteins include neurotransmitters (substance P and calcitonin gene-related peptide), receptors (bradykinin R), channels (TRPV1, ASIC-3, and sodium channels), transcription factors (ATF-3), and structural molecules (neurofilaments and the sodium-channel-anchoring molecule p11).[34] Additionally, NGF can modulate the trafficking and insertion of sodium channels such as $Na_V1.8$ and TRPV1 in sensory neurons and modulate the expression profile of supporting cells in the dorsal root ganglia (DRG) and peripheral nerves, such as nonmyelinating Schwann cells and macrophages.[10,34] Anti-NGF antibody therapy may be particularly effective in blocking bone cancer pain because NGF appears to be integrally involved in the upregulation, sensitization, and disinhibition of multiple neurotransmitters, ion channels, and receptors in the primary afferent nerve and DRG fibers that synergistically increase nociceptive signals originating from the tumor-bearing bone.

*Anti-NGF antibody therapy may be particularly effective in blocking bone cancer pain*

To test the hypothesis that blocking NGF from binding to its cognate receptor TrkA is efficacious in reducing bone cancer pain, the analgesic efficacy of a murine anti-NGF monoclonal antibody was evaluated in two animal models of bone cancer.[35,36] These models included the primarily osteolytic mouse osteosarcoma line, which expresses high levels of NGF,[36] and the primarily osteoblastic canine ACE-1 prostate, where NGF expression is undetectable.[35] 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 10 mg/kg of morphine sulfate.[35,36] These data suggest that therapeutic targeting of NGF or its cognate receptor TrkA may be useful in blocking bone cancer pain, whether or not the tumor that has metastasized to bone expresses NGF. Presumably, in the case where the tumor cells

themselves do not express NGF, it is the tumor stromal cells that are expressing and secreting NGF, because tumor stromal cells comprise 2–60% of the total tumor mass. Currently, a fully humanized monoclonal antibody to NGF known as tanezumab has been tested in human patients with osteoarthritis, and this therapy was effective at reducing arthritis-related pain.[37] Human clinical trials evaluating tanezumab's effects at reducing bone cancer pain in patients with advanced breast or prostate cancer are scheduled to commence in mid-2009.[38,39]

## Neuropathic Component of Bone Cancer Pain

Sensory and sympathetic neurons are present within the bone marrow, mineralized bone, and periosteum, and all these compartments are ultimately affected by fractures, ischemia, or the presence of tumor cells. Therefore, sensory fibers in any of these tissues may play a role in the generation and maintenance of bone cancer pain.

In examining the changes in the sensory innervation of bone that are induced by the primarily osteolytic sarcoma cells, researchers have observed sensory fibers at and within the leading edge of the tumor in the deep stromal regions of the tumor.[40] Additionally, these sensory nerve fibers displayed a discontinuous and fragmented appearance, suggesting that following initial activation by the osteolytic tumor cells, the distal processes of the sensory nerve fibers were injured by the invading tumor cells.[40] In contrast, an examination of the sensory innervation of bone following injection of the primarily osteoblastic prostate cancer cells suggests that there is simultaneous injury and sprouting of sensory fibers into the tumor cells and newly formed woven bone.[15]

*Several therapies that attenuate bone cancer pain may also reduce tumor growth and tumor-induced bone remodeling*

The tumor-induced injury and remodeling of sensory nerve fibers in these bone cancer pain models were accompanied by an increase in ongoing and movement-evoked pain behaviors, an upregulation of galanin by sensory neurons that innervate the tumor-bearing femur, upregulation of glial fibrillary acidic protein and hypertrophy of satellite cells surrounding sensory neuron cell bodies within the ipsilateral DRG, and macrophage infiltration of the DRG ipsilateral to the tumor-bearing femur.[10] Similar neurochemical changes have been described following peripheral nerve injury and in other noncancerous neuropathic pain states.[41] Additionally, chronic treatment with gabapentin in the sarcoma model attenuated both ongoing and movement-evoked bone cancer-related pain behaviors but did not influence tumor growth or tumor-induced bone destruction.[40] These results suggest that even when the tumor is confined within the bone, a component of bone cancer pain is due to tumor-induced injury or remodeling of sensory and sympathetic nerve fibers that normally innervate the bone. Currently, clinical trials are assessing the effects of pregabalin on attenuating chronic bone pain related to metastatic tumors.[42]

## Conclusions

Over the last decade, progress has been made in laying the foundation for a mechanism-based understanding of the factors that drive bone cancer pain. Interestingly, several therapies that attenuate bone cancer pain may also reduce tumor growth and tumor-induced bone remodeling. Thus, bisphosphonates are commonly used to treat bone cancer pain, and other therapies including denosumab (anti-RANKL; Amgen), tanezumab (anti-NGF; Pfizer), and pregabalin (Pfizer) are in mid- to late-stage clinical trials. Currently, we are beginning to understand the mechanisms that drive bone cancer. If this progress can be sustained and expanded, these advances have the potential to enlarge the repertoire of therapies available to treat bone cancer pain and significantly improve the quality of life, functional status, and survival of patients with bone cancer.

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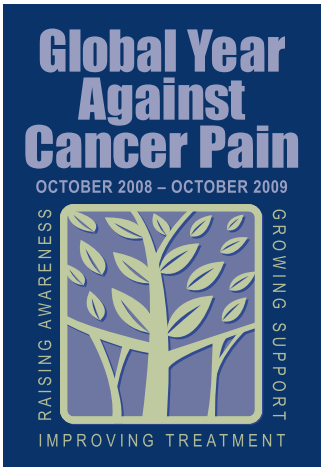


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