

Biology of Bone Cancer Pain

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Abstract Bone cancer pain is a devastating manifestation of metastatic cancer. Unfortunately, current therapies can be ineffective, and when they are effective, the duration of the patient's survival typically exceeds the duration of pain relief. New, mechanistically based therapies are desperately needed. Study of experimental animal models has provided insight into the mechanisms that drive bone cancer pain and provides an opportunity for developing targeted therapies. Mechanisms that drive bone cancer pain include tumor-directed osteoclast-mediated osteolysis, tumor cells themselves, tumor-induced nerve injury, stimulation of transient receptor potential vanilloid type 1 ion channel, endothelin A, and host cell production of nerve growth factor. Current and future therapies include external beam radiation, osteoclast-targeted inhibiting agents, anti-inflammatory drugs, transient receptor potential vanilloid type 1 antagonists, and antibody therapies that target nerve growth factor or tumor angiogenesis. It is likely that a combination of these therapies will be superior to any one therapy alone.

Patients with malignant tumors that have metastasized to bone are frequently confronted with poor quality of life. Skeletal complications as sequelae of metastatic disease manifest themselves in ~70% of patients with advanced breast or prostate carcinoma (1). Skeletal metastases are discovered in >90% of patients who die of breast or prostate carcinoma (1). Bone cancer pain is one of the most common symptoms presented by patients with cancer (2–6). Metastatic breast and prostate carcinomas are principal contributors to the prevalence of cancer-induced bone pain. Mechanical allodynia is the painful perception of mechanical stimuli that are not normally perceived as noxious. With this bone cancer pain, this acute form of movement-evoked pain can be generated by modest limb use, coughing, or turning in bed and has diminished responsiveness to conventional therapeutics.

Animal Models of Bone Cancer Pain

Experimental models of bone cancer pain have been developed in mice and rats. These models study tumors at different anatomic sites and of varied histologic origin. Contemporary experimental models are based on direct injection of cancer cells into the medulla of the femur, humerus, and calcaneus (7–15).

Direct local intramedullary injection of tumor cells is preferred over systemic administration of tumor cells via i.v. or intracardiac routes because the skeletal site where the tumor

develops is known, allowing for analysis of corresponding behavioral and neuroanatomic segments. In addition, intra-medullary injection permits simultaneous and precise quantitative evaluation of site-specific pain behaviors, tumor growth, bone destruction, bone microenvironment, and neurochemistry. Bone cancer pain has been studied using a rat breast carcinoma model (MRMT-1), murine fibrosarcomas (2472), murine breast carcinomas (4T1), hepatocellular carcinomas (HCa-1), and murine melanoma (B16).

Assessment of cancer-induced bone pain in experimental animal models has been done based on behavioral analysis and neurochemical markers of pain, radiographic imaging, and histology. Ongoing pain is measured in animal models by quantification of spontaneous guarding and flinching or the duration and frequency that a mouse holds the tumor-affected limb aloft during a predetermined observation period. Movement-evoked bone pain is assessed by limb use in an open field and forced ambulation.

Radiographic and histologic analysis of osteolytic tumors have consistently shown that mature, multinucleated osteoclasts are stimulated by release from tumor cytokines and growth factors. Osteolytic bone destruction has been correlated to pain behaviors, neurochemical changes, and cellular changes in the spinal cord (16–18).

Neurochemistry and Bone Cancer Pain

Bone contains a highly concentrated mosaic of primary sensory afferent and sympathetic fiber innervation embedded in the periosteum and intramedullary bone (Fig. 1; refs. 8, 19–22). Cellular and neurochemical characteristics of chronic pain can be detected in peripheral nerves within the dorsal root ganglia and at the site of primary sensory afferent innervation of the spinal cord. Central nervous system abnormalities have been detected by evaluation of the neurochemistry and neural composition of the spinal cord (Fig. 2).

Evidence from experimental animal models suggests that the neurochemical and cellular characteristics of bone cancer pain

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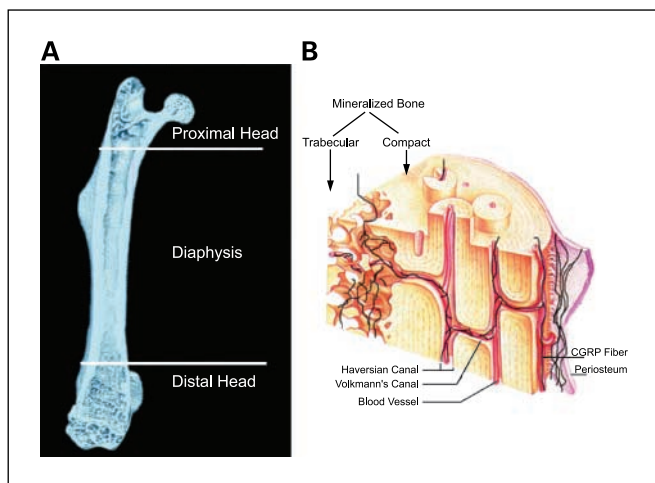


Fig. 1. Distribution of nerve fibers in bone. *A*, microcomputed tomography scan of the mouse femur subdivided according to proximal head, diaphysis, and distal head via presence of intramedullary trabecular bone. *B*, sensory fiber localization in periosteum, mineralized bone, and bone marrow. Sensory fiber concentration per unit area is greatest in the periosteum and concentrated less in the mineralized bone. The schematic is adapted from Marieb and Mallat, 1997. Reprinted with permission from Mach DB, Rogers SD, Sabino MC, Luger NM, Schwei MJ, Pomonis JD, Keyser CP, Clohisy DR, Adams DJ, O'Leary P, Mantyh PW. Origins of skeletal pain: sensory and sympathetic innervation of the mouse femur. *Neuroscience* 2002;113:155–66. © 2002 IBRO.

are unique when compared with inflammatory or neuropathic pain. Bone cancer pain causes reorganization and sensitization of the central dorsal horn of the spinal cord. This condition is manifested as increased expression of the prohyperalgesic peptide dynorphin, enhanced neuronal activity monitored by elevated c-Fos expression, and profound astrocytosis (23–25). Data indicate that painless stimuli can stimulate release of substance P from primary afferent sensory neurons of cancerous hind limbs, terminating in lamina I of the spinal cord (26). In contrast to inflammatory and neuropathic diseases, bone cancer pain does not produce significant expression of substance P and CGRP markers in the dorsal horn of the spinal cord or GAL and NPY in the primary sensory afferent neurons. Importantly, however, expression of glial fibrillary acidic protein, an astrocyte-specific cellular protein found in the supporting glial cells of the spinal cord, increases markedly in bone cancer pain.

Therapies for Cancer-Induced Bone Pain

Most patients with skeletal metastases experience bone pain. Of these patients, 54% receive only temporary pain relief with treatment (27). Permanent pain relief is often not achieved and continues to challenge physicians. Current therapies focus on eliminating tumor proliferation, reducing tumor-induced bone loss, intervening surgically to stabilize painful bones infiltrated with skeletal metastases, and administering powerful pain medications. Treatment regimens can include monotherapy or concurrent combinations of nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, chemotherapy, radiotherapy, nitrogen-containing bisphosphonates, and opioids. Medical management of bone cancer pain typically begins with anti-inflammatory drugs or cyclooxygenase-2 inhibitors that are aimed at alleviating inflammatory states associated with bone pain. The potency of cyclooxygenase-2 inhibitors versus anti-

inflammatory drugs is similar, but cyclooxygenase-2 inhibitors produced fewer gastrointestinal side effects.

Eradication of the tumor is usually approached with chemotherapy and radiotherapy. External beam radiation is one of the most effective treatments found to alleviate tumor-induced bone pain, with 90% of patients receiving some pain relief and 50% of patients having complete relief. Unfortunately, >50% of patients who undergo radiation treatment and obtain pain relief will experience a relapse of pain equivalent to pretreatment levels (28). The exact mechanism of radiation-induced pain relief is unknown. Hoskin et al. (29) suggested that decreased activity of osteoclasts in the bone microenvironment after radiation treatment was responsible for decreased bone destruction and was a predicting factor in the decreased pain response after radiation. More recently, Goblirsch et al. (30) suggested reduced tumor burden and reduced osteolysis as the mode through which radiation improved cancer-induced bone pain (Fig. 3; ref. 30).

Administration of bisphosphonates and/or surgical stabilization addresses the painful, fragile condition of bones affected by tumor-induced bone loss and skeletal metastases.

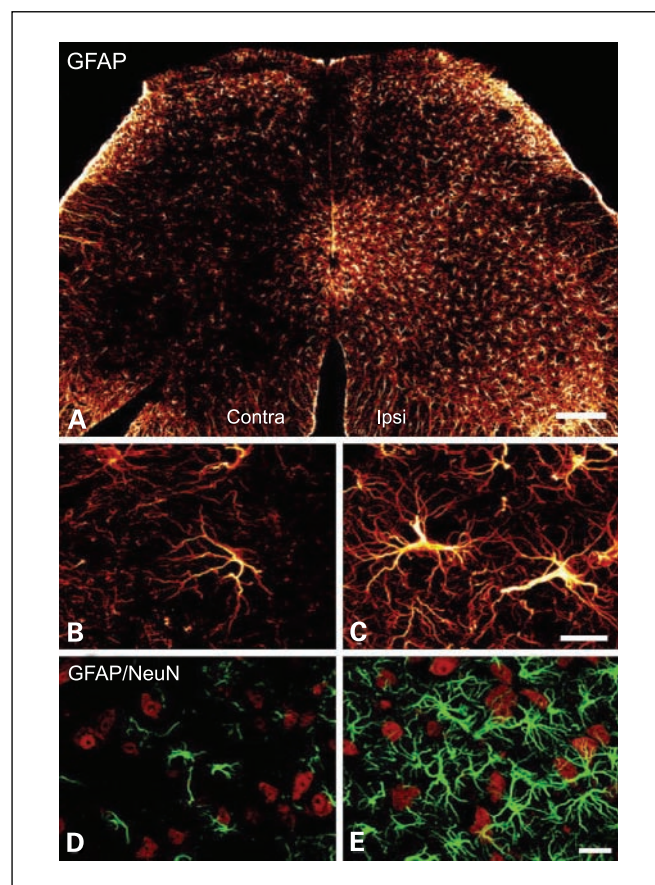


Fig. 2. Spinal cord astrogliosis as an indicator of bone cancer pain. Confocal image showing the profound unilateral discrepancy of glial fibrillary acidic protein (GFAP) staining (bright orange) in coronal sections of the fourth lumbar segment of the spinal cord after intramedullary injection of osteolytic sarcoma cells into the femur. Glial fibrillary acidic protein up-regulation, a marker of astrocyte hypertrophy, is nearly exclusive to the ipsilateral spinal cord of the tumor-bearing femur. Reprinted with permission from Schwei MJ, Honore P, Rogers SD, Salak-Johnson JL, Finke MP, Ramnaraine ML, Clohisy DR, Mantyh PW. Neurochemical and cellular reorganization of the spinal cord in a murine model of bone cancer pain. *J Neurosci* 1999;19:10886–97. © 1999 Society for Neuroscience.

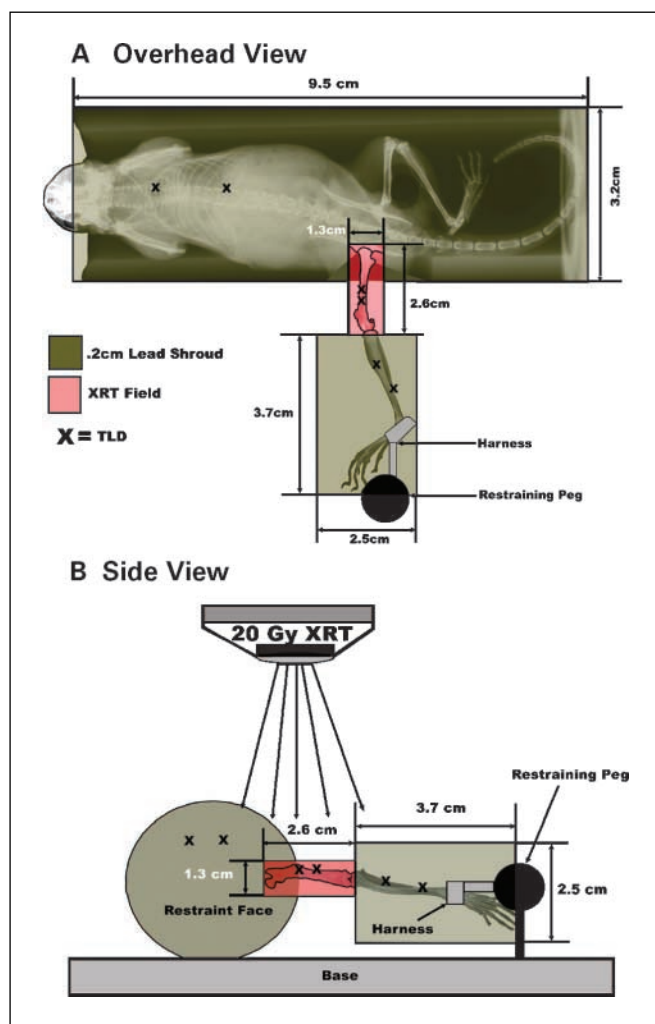


Fig. 3. Murine model of radiation treatment for bone cancer pain. A schematic depiction of the lead-lined restraint used to deliver a localized dose of radiation to tumor bearing femora. Reprinted with permission from Goblirsch M, Mathews W, Lynch C, Alaei P, Gerbi BJ, Clohisy DR. Radiation treatment decreases bone cancer pain, osteolysis, and tumor size. *Radiat Res* 2004;161:228–34. © 2004 Radiation Research Society.

Bisphosphonates, used initially to treat humoral hypercalcemia of malignancy, have shown promise at decreasing cancer-induced skeletal complications. The suggested mechanism of action is a direct inhibition of osteoclasts and osteoclast precursor cells (31–35). Recent reports have shown that bisphosphonate treatment can significantly reduce osteoclasts and osteolytic destruction of bone (36, 37). The nitrogen-containing bisphosphonate alendronate has been shown to alleviate ongoing and movement-evoked pain in a murine model of femoral cancer (18). The suggested mechanism for reduction in pain behaviors is produced by inhibition of bone resorption and mechanical stabilization (8, 17). It has also been hypothesized that osteoclast inhibition causes an increased bone-tumor microenvironment pH, resulting in a loss of acid-sensing ion channel stimulation (38, 39).

Chronic pain unresponsive to anti-inflammatory agents, chemotherapy, radiotherapy, surgery, and/or bisphosphonates is typically combated with strong pain medications. Opioid management of advanced bone cancer pain is common and

effective for pain relief. Unfortunately, opioid doses required to attenuate bone pain (120 mg/kg daily) can produce undesirable side effects, such as confusion, somnolence, and constipation. These side effects can severely diminish overall quality of life (40, 41). Within 4 weeks after seeing their physician, 73% of terminally ill patients receiving opioid treatment reported pain that was moderate to severe, and 40% of those patients with severe pain requested an increase in opioid treatment (2). Because opioids do not directly target the source of pain but act systematically via the central nervous system, the negative repercussions to organ systems can contribute significantly to poor quality of life.

Significant progress has been made recently in experimental models that examine potential new therapies. The link between osteolysis and bone cancer pain was shown in studies where reduced ongoing and movement-evoked pain was noted after OPG-Fc was delivered to block bone cancer-induced bone pain and osteolysis (42, 43). Clinical trials are currently under way using a humanized antibody against RANKL. Other laboratory research indicates that the transient receptor potential vanilloid type 1 ion channel, endothelin A, and anti-nerve growth factor therapies relieve bone cancer pain (Fig. 4; ref. 44). It has been shown, using transient receptor potential vanilloid type 1 antagonists and transient receptor potential vanilloid type 1 knock-out mice, that this acid-sensing ion channel contributes to bone cancer pain (45). Endothelin A, a receptor antagonist, and treatment with anti-nerve growth factor antibody have been shown to reduce bone cancer pain (12, 46).

Conclusion

Cancer-induced bone pain is a complex pain condition. Novel initiatives pursuing the etiology and treatment of bone cancer pain are requisite to identify the mechanistic origins of this debilitating pain condition. Recent work using experimental animal models that mimic patient-like states have proven valuable by initiating study of bone cancer pain. From this research, induction of peripheral and central sensitization of the nervous system has been shown to originate from

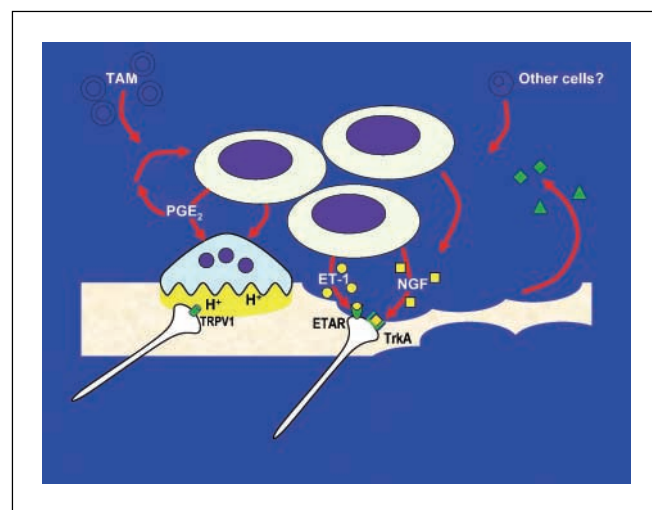


Fig. 4. Laboratory research indicates that the transient receptor potential vanilloid type 1 (TRPV1) ion channel, endothelin A (ET-A), and anti-nerve growth factor (anti-NGF) therapies relieve bone cancer pain.

skeletal cancers. Continued investigations to elucidate molecular markers and mechanisms through which sensitization occurs will be important. Use of current and emerging animal models to test the efficacy of emerging therapies will direct future clinical management of this dreaded condition.

Open Discussion

Dr. Roodman: Is innervation increased when a tumor is involved?

Dr. Clohisy: At the time points we have looked at, it has not increased. If you look in the bone at the nerves, they are injured. If you look in the dorsal root ganglion, you see transcription factors that are indicative of cellular crisis.

Dr. Roodman: Is NGF required for maintaining nerve function and increasing nerve growth?

Dr. Clohisy: Not in adults.

Dr. Guise: You stated that skeletal fragility is painful. Do you mean that in the absence of fractures?

Dr. Clohisy: In the absence of at least a clinically detectable fracture, yes.

Dr. Coleman: The osteolytic component is painful, the tumor causes pain, and the mechanics cause pain. What about the osteoblastic loop? Do osteoblasts cause pain or does the new bone formation contribute to pain in any way? In other words, can we leave the osteoblasts alone?

Dr. Clohisy: We can leave the osteoblasts alone for now, until we get better therapies. In a prostate cancer paper published in *Cancer Research* this week (Halvorson et al. *Cancer Res.* 2005;65:9426-9435), the authors looked at a more mixed tumor, both blastic and lytic. This was a very painful tumor, and pain was eliminated almost completely by anti-NGF therapy. It looks like NGF almost exclusively drives the pain. We know that the NGF can be produced by tumor cells and or host cells *in vivo* at sites of painful bone cancers. It is possible and interesting to speculate that osteoblasts may produce NGF.

Dr. Vessella: In osteoblastic disease, are there any data to show that the new bone pinches the nerves or compresses the nerves?

Dr. Clohisy: I don't know the answer to that question. If we had an excellent bone-forming model, we would be interested in looking at this.

Dr. Weilbaecher: Are you implying that in the osteoblastic metastasis the pain is from the osteoclastic activity?

Dr. Clohisy: And/or from the tumor itself and/or from inflammatory cells or perhaps osteoblasts making NGF.

Dr. Weilbaecher: Do you feel that there is evidence that the blasts themselves directly remodel the spinal cord and recruit pain fibers?

Dr. Clohisy: No.

Dr. Coleman: Why do you think the pain relief in patients who undergo kyphoplasty is way out of proportion to what you are doing mechanically?

Dr. Clohisy: There are mechanoreceptors in bone, and they could be based on the configuration of the bone that is being innervated. When kyphoplasty is performed, at a minimum it stabilizes bone and at a maximum it restores the bone's shape.

Dr. Pearce: Trk tyrosine kinases, high affinity receptors for neurotrophins such as NGF, are expressed by prostate carcinoma cells. As Trk receptors initiate pro-survival signals, Trk kinase inhibitors have been used to treat prostate cancer in phase 2 trials. However, I am not aware of any change in the pain appreciated by the patients. Has anybody had experience with that?

Dr. Clohisy: It would be interesting if they looked at pain in those trials and, if they did, how they looked at it?

Dr. Suva: Do you know how much tumor you need to have in the bone to get pain?

Dr. Clohisy: At 7 days after inoculation of the tumor, mice will always have pain both behaviorally and neurochemically. At that time, there is no appearance, on X-ray, of a tumor, and histologically, there is no disruption of the cortex or involvement of the periosteum.

Dr. Suva: That sounds like bone resorption. If you increase their bone resorption, can you get any detectable pain measures in those mice?

Dr. Clohisy: I don't know. One hypothesis is that the nerves react to the rate of bone resorption. If it's gradual, the nerve can retract or modify itself so it doesn't overreact if it comes in contact with the resorption bay. Although it's a nice theory that the osteoclasts are stimulating the acid-sensing ion channels, it could be that the acid microenvironment of the tumor-bone microenvironment is what's actually stimulating the ion-sensing channels, not specifically in the resorption bay.

Dr. Suva: Has anyone done studies in mice and showed that when you increase bone mass after a bone loss event that they have a return to normal amounts of pain?

Dr. Clohisy: I don't think that has been done. One of the problems with the model is that it has to be localized pain. We haven't worked on total body or total skeletal pain measures.

Dr. Roodman: You could use op/op mice, for example, that are a little older so that they are no longer as osteopetrotic as they were when they were young.

Dr. Clohisy: That's interesting, because our tumors are syngeneic with some of those mouse lines.

Dr. Roodman: If you do them young enough, you don't have as much severe osteopetrosis as you do with older animals. You can begin to sort out contributions of resorption versus contributions of tumor growth versus NGF.

Dr. Suva: Couldn't you do something like compare a bisphosphonate to a inhibitor, where one is going to block acidification of the lacunae versus generic suppression of bone resorption?

Dr. Clohisy: The challenge is trying to figure out where to go next.

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