Review Article

Bone Cancer Pain

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Abstract

In 2012, the International Agency for Research on Cancer reported 14.1 million new cancer cases, 8.2 million cancer deaths, and 32.6 million people living with cancer. Cancer pain not only causes significant suffering but also contributes to a decreased quality of life, functional status, and greatly increases health-care costs. The bones are a common site for metastases, especially tumors involving breast, lung, prostate, and kidneys. This can lead to significant pain, pathological fractures, compression of the spinal cord, poor quality of life, and increased mortality. Pathophysiology of cancer-induced bone pain is complex and has neuropathic and nociceptive characteristics. The aim of the treatment of bone metastases is palliating painful symptoms and preventing progression of skeletal-related events. A multimodal approach including various cancer therapies, analgesic and adjuvant agents, and interventional modalities should be used. This review focuses on the pathophysiology of bone cancer pain and pharmacological and non-pharmacological modalities that reduce bone cancer pain.

Keywords: Bone cancer pain, bone metastases, cancer pain

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Burden Of Bone Cancer Pain

In 2012, the International Agency for Research on Cancer reported 14.1 million new cancer cases, 8.2 million cancer deaths, and 32.6 million people living with cancer.[1] According to the American Cancer Society, there will be an estimated 1,685,210 new cancer cases diagnosed and 595,690 cancer deaths in the US, at the end of 2016.[2] For many patients, pain is the first sign of cancer, and most individuals will experience moderate-to-severe pain during the course of their disease.[3] Cancer pain can be present at any time during the course of the disease; it generally increases with disease progression so that 75%–90% of patients with metastatic or advanced stage cancer will experience significant cancer pain.[3,4] As such cancer pain not only causes significant suffering but also contributes to a decreased quality of life, functional status and greatly increases health-care costs.

Some of the most common tumors (breast, prostate, thyroid, kidney, and lung) have a strong predilection to simultaneously metastasize to multiple bones.[5,6] It has been reported that tumor metastases to the skeleton affect over 400,000 individuals in the United States of America annually. 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.[6,7]

Sensory Innervation of Bone

Previous studies have shown that the human and rodent skin is innervated by thickly myelinated sensory nerve fibers (A-beta), thinly myelinated sensory nerve fibers (A-delta) and both classes of unmyelinated sensory nerve C-fibers: the peptide-rich CGRP + nerve fibers and peptide-poor nerve fibers.[8-11] Studies using either transgenic animals or retrograde tracers showed that the peptide-poor population of C-fibers does not appear to innervate human[10] and rat intervertebral discs,[9] rat hip,[12] rat wrist joint,[13] cat humerus,[14] and mouse femur.[8]

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In terms of A-beta nerve fibers expression in bone tissue, previous pre-clinical studies using electron microscopy demonstrated that few, if any, thickly myelinated nerve fibers innervate the in cat humerus periosteum[14] and dog tibia bone marrow.[15] In support with these anatomical studies, electrophysiological recordings from periosteal afferent nerve fibers arising from the cat humerus bone demonstrated that all nerve fibers have conduction velocities in the range of C-fibers and A-delta nerve fibers.[16] Taken together, these studies suggest that bone is primarily innervated by thinly myelinated sensory nerve fibers (presumably A-delta) and peptide-rich CGRP + nerve fibers. Thus, targeting this restricted population may provide a unique therapeutic opportunity for developing novel analgesics that can bone cancer pain.

Involvement of Osteoclasts-Mediated Acidosis in The Development of Bone Cancer Pain

Studies in both humans and animals have suggested that osteoclasts (the cells that breakdown bone) play a significant role in cancer-induced bone loss[17] and that osteoclasts contribute to the etiology of bone cancer pain.[18,19] 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.[20] Both osteolytic (bone destroying) and osteoblastic (bone forming) cancers are characterized by osteoclast proliferation and hypertrophy.[21-23] Thus, osteoclast-mediated bone remodeling results in robust production of extracellular protons,[24] which are known to be potent activators of nociceptors.[24] 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.[25] Another method that is highly effective at reducing tumor-induced osteoclast bone resorption in both animals and humans is by interfering with the binding of RANKL to RANK, which is required for osteoclast proliferation and maturation. Within 2 days of administration of therapies that interfere with RANKL binding to RANK (such as osteoprotegerin or denosumab), there is an almost complete loss of activated osteoclasts, a marked reduction in plasma markers of bone resorption, and a significant attenuation of bone cancer pain.[26]

Treatment of cancer-induced bone pain

Cancer-induced bone pain is multifactorial, and different modalities can be applied to achieve optimal pain control and improve the quality of life. The goal of treatment is palliation of symptoms as well as prevention of progression of skeletal-related events (SRE). This includes multimodal therapies anticancer therapies (radiotherapy, endocrine treatments, chemotherapy, targeted therapies, and radioisotopes), optimizing bone health, pharmacologic (analgesic and adjuvant agents), and interventional modalities.[27-29] Bone cement augmentations and orthopedic interventions may be necessary for structural complications if bone destruction or nerve compression occur.[20]

Bone Health in Cancer Patients with Bone Metastases

Bone health in cancer patients is of increasing clinical importance because of its morbidity. Bone metastases can lead to complications including fractures, severe pain, and hypercalcemia. Pathologic fractures, spinal cord compression, impending fracture, and severe pain are known as SRE.[30] Because of the treatment cancer *per se*, some of these treatments have also effect on reproductive hormones, which are critical for the maintenance of normal bone remodeling. This endocrine disturbance results in moderated bone loss and increased risk of osteoporosis. Finally, emerging data demonstrates that, since bone marrow micro-environment is intimately involved in cancer dissemination, the use of bone-targeted treatments can reduce metastasis to bone.[31]

Pharmacological Treatment

Antiresorptive therapy

Bisphosphonates

Bisphosphonates (BPs) are analogs of pyrophosphate, with carbon replacing the central oxygen. BPs decrease bone resorption and increase mineralization by specifically inhibiting osteoclast activity. All BPs accumulate in the mineral portion of the bone matrix and are released during bone resorption. They are embedded in bone, released in the acidic environment of the resorption lacunae under active osteoclasts and are taken up by them. Therefore, biphosphonates interrupt the "vicious cycle" of tumor-mediated osteolysis by inhibiting the activity of bone-resorbing osteoclasts and inducing their apoptosis.[32] There are two types of BPs. Nonnitrogen-containing BPs are metabolized by osteoclasts into nonhydrolyzable cytotoxic ATP analogs. On the other hand, nitrogen-containing BPs inhibit the mevalonate pathway after internalization by osteoclasts.[33]

Antiresporptive therapy can be indicated to prevent SREs and for prevention of treatment-induced bone loss. Some authors have proposed that BPs can be indicated for the prevention of breast or prostate cancer metastases. Preclinical studies using *in vivo* model systems have demonstrated the ability of zoledronic acid, ibandronate, and olpadronate before tumor cell injection to prevent homing of tumor cells to bone and cause direct induction of tumor cell death in bone, although there is no regulatory approval.[31,34] There are specific indications of BPs for the prevention of SREs[30,31] some are summarized in Table 1.

The main adverse events associated with BP therapy are acute-phase reactions such as gastrointestinal toxicity, renal toxicity, and osteonecrosis of the jaw. Osteonecrosis of the jaw is a rare but serious complication, which appears as painful oral ulcerations that expose underlying bone. Risk factors for osteonecrosis of the jaw include treatment with intravenous

Table 1: Biphosphonates for bone health in cancer

Tumor type	Bisphosponate
Solid tumors and multiple myeloma	Zoledronic acid 4 mg IV every 3-4 weeks
Breast cancer and multiple myeloma	Pamidronate 90 mg IV every 3-4 weeks
Breast cancer	Ibandronate 50 mg postoperative daily Ibandronate 6 mg IV monthly

IV: Intravenous

BPs, dental extractions, and presence of oral infection. Therefore, it is recommended to perform a dental examination in all patients that are going to receive BPs and in patients who have been given BPs within the last 3 months.[35]

In multiple myeloma, tumor cells originate in the bone marrow and either alone or through interactions with the bone marrow stromal cells, also alter bone homoeostasis. BPs effectively reduce SREs in multiple myeloma patients. Clinical data have confirmed preclinical observations that BPs may have antimyeloma activity. Survival advantage varies in different patient subpopulations: those with no fractures at baseline in clodronate studies, those who received second-line therapy in pamidronate studies, or finally those with high bone resorption or bone disease at baseline in zoledronate studies. Up to 12% with advanced multiple mieloma had a 12% improvement in relapse-free survival. Patients in another trial comparing clodronate versus placebo presented a decreased proportion of SREs, but only patients without vertebral fractures at study entry had a benefit in overall survival (*post hoc* analysis). Currently, zoledronate and pamidronate intravenously are the BPs used in multiple myeloma patients with bone disease.

Monoclonal antibodies

Denosumab is a human IgG2 monoclonal antibody that inhibits binding of the receptor activator of nuclear factor kappa-B ligand (RANKL, part of the tumor necrosis factor family) to RANK receptors located on the surface of osteoclasts and their precursors. This inactivation prevents the formation, function, and survival of osteoclasts, which then reduces bone resorption, allowing for growth in cortical and trabecular bone.[36] Denosumab treatment in clinical trials showed sustained reductions from baseline levels of multiple biomarkers of bone resorption and bone formation. These biomarkers provide evidence for the efficacy of therapies and their prognostic value; elevation of these biomarkers is generally correlated with SREs, disease progression, and death in patients with bone metastases. Steady state serum levels of denosumab are reached by 6 months following multiple 120 mg subcutaneous doses administered every 4 weeks. Denosumab pharmacokinetics are not affected by renal impairment even when patients are on hemodialysis. Among the adverse events of denosumab, patients can experience are hypocalcemia and osteonecrosis of the jaw.

Currently, phase III clinical trials are underway for assessing Denosumab's effects on attenuating cancer-induced bone loss in breast and prostate cancers,[37] SREs (pain, fracture) due to the spread of cancer to the bone in multiple myeloma and multiple solid tumors, as well as the Denosumab's potential to delay bone metastases in prostate cancer.[38]

Tanezumab is a recombinant monoclonal antibody that binds to local tissue NGF and prevents its interaction bnwith TrkA receptors. One study comparing placebo with tanezumab for painful bone metastases showed no difference.[39]

Analgesics per WHO ladder

The WHO ladder consists in a three-step model for the medical management of cancer pain. If pain occurs there should be prompt oral administration of drugs in the following order: for mild pain, nonopioids (nonsteroidal anti-inflammatory drugs [NSAIDs], and paracetamol), then as necessary for moderate pain, mild opioids (tramadol and codeine), and then strong opioids such as morphine for persisting pain. In all three steps, adjuvants can be used. To maintain freedom from pain, drugs should be given by the clock, rather than on demand.[29] There is not good high quality evidence supporting the use of NSAIDs with or without the combination of opioids.[40] There is also the risk of GI bleeding, renal injury, cardiovascular events, or bleeding associated with the use of NSAIDs. Paracetamol is less efficacious in cancer-induced bone pain. Opioids remain a mainstay analgesic for moderate-to-severe cancer pain and used for background as well as breakthrough pain.[41]

Adjuvant analgesics

Corticosteroids are commonly used adjuvant analgesics for cancer-induced bone pain and spinal cord compression. The evidence for efficacy of steroids for bone cancer pain is weak, WHO recommends use of corticosteroids as adjuvant agents if indicated.[29] Dexamethasone is preferred due to its long half-life and low mineralocorticoid activity. Gabapentenoids (gabapentin and pregabalin) are commonly used for neuropathic pain. Animal studies have shown efficacy in cancer induced bone pain, though this has not translated to human studies. A systematic review showed no evidence that calcitonin was effective in controlling complications from bone metastases; or improving quality of life.[42]

Radiotherapy

Local external beam irradiation is highly effective for bone pain. Overall, response rates of around 85% are reported, with complete relief of pain achieved in one-half of patients. Pain relief usually occurs rapidly, with more than 50% of responders showing benefit within 1–2 weeks. If improvement in pain has not occurred by 6 weeks or more after treatment, it is unlikely to be achieved. Targeted radiotherapy with therapeutic radioisotopes has theoretical advantages over external beam radiotherapy (EBRT) in that the radiation dose may be delivered more specifically to the tumor and normal tissues partially spared unnecessary irradiation.[31] Follicular carcinoma of the thyroid commonly metastasizes to bone and the treatment of bone metastases with 131-iodine is well established. The objective of treatment is to achieve

sufficient concentration of radioactive iodine in tumor areas for treatment efficacy.[43] Unlike EBRT, Radium-223 has systemic uptake, with the potential to address several bone metastases concurrently and provides overall survival benefit. Radiopharmaceutical radium 223 chloride provides a high dose of radiotherapy to cells within 1 μm of the bone surface with minimal systemic effects.[44]

Percutaneous Interventional Management of Bone Metastases

Vertebroplasty

Metastasis to the spine generates serious back pain and compression fractures that can cause considerable morbidity, as decreased mobility, kyphosis, neurologic complications, and respiratory compromise. Treatment decision should be based on different factors as the local extent of tumor, the neurological findings, overall prognosis for survival, the histology of the primary tumor, and the extent of metastasis.[45] The conventional treatment of spinal metastases is open surgery, however, it can often cause considerable trauma, result in complications, and delay treatment of the primary disease owing to prolonged hospitalization. Besides, open surgery is not suitable for the treatment of multiple metastasic lesions of spinal tumors.

Percutaneous vertebroplasty (PVP) and kyphoplasty (PKP) are two techniques used to treat painful VCFs. PVP is the percutaneous injection of a vertebral body with bone cement, generally polymethylmethacrylate (PMMA). PMMA has been used in orthopedics since the late 1960s.[46] Percutaneous VP was first reported by a French group in 1987 for the treatment of painful hemangioma.[47] Since then, the indications for VP have expanded to include osteoporotic compression fractures and painful vertebral metastasis. Percutaneous KP is a modification of VP; it involves the percutaneous placement of balloons (called "tamps") into the vertebral body with an inflation/deflation sequence to create a cavity prior to PMMA injection. Percutaneous KP may restore vertebral body height and reduce the kyphotic angulation of the compression fracture prior to injection.[48] PVP can treat spinal osteolytic lesions that generate osseous destruction and compression fractures of vertebral bodies. While radiotherapy requires 2–4 weeks to take effect, does not achieve complete pain relief and does not stabilize vertebral fractures, PVP is an effective procedure for achieving prompt pain control and preventing further vertebral collapse an spinal cord compression.[49]

PVP and PKP are considered effective procedures to achieve prompt pain control and prevent further vertebral collapse in patients with vertebral metastasis. Complete and partial pain relief is reported in 73%–97% of treated patients.[50]

Among the major complications of this procedure are cement leakage into the canal or nerve root foramen, this can result in spinal cord compression or radiculopathy and embolic events caused by cement, marrow fat, or tumor entering the circulation. According to the Society of Interventional Radiology, the major complication rate of PVP is <1% and reaches approximately 5% in tumor patients. Cement leakage has been documented on radiographs in 30%–72.5% of patients and on computed tomography (CT) in 87.9%–93% of patients.[50]

A retrospective study evaluated the effectiveness of PVP on the prevention of progression of local recurrence in patients with spinal metastases from breast cancer.[51] They found a rate of local tumor progression/recurrence of the vertebrae treated by vertebroplasty was 14% (19 of 137), and no statistically significant correlation between the rate of cement filling and progression/local recurrence after vertebroplasty was found. No influence of radiotherapy in preventing local progression/recurrence was noted. However, distant new bone metastases were observed in 46 out of 55 patients (85%). It is postulated that bone cement is toxic to cells when it is not completely polymerized with an effect relatively similar to the effect of alcohol. Additionally, the energy released during cement polymerization may cause thermal injury to the cells. Exothermic polymerization of PMMA can reach temperatures over 75°C with a cytotoxic effect of 3 mm around the cement. It also has been proven that PMMA injection can lead to bone tissue devascularization; therefore, this mechanism may also participate to the antitumor effect of bone cement.[51] Analysis of pathological findings in patients in whom PMMA has been injected has demonstrated a macro and microscopic rim of tumor necrosis 6 months after vertebroplasty/tumor injection, which seems to extend outside the limits of the cement.

Femoroplasty

The vast majority of cancer patients with bone metastases are in advanced stages of their disease. Some of these metastatic bone lesions involve long bones such as the femur, but there are few studies examining minimally invasive treatments for these areas.

At the femoral level, when the PMMA bone cement is used, it solidifies and permits stabilization of the bone structure and coxofemoral articulation. When PMMA, is injected, a thermal action produced by the cement, reduces the metastatic activity, and it is suggested that this probably inhibits the regional nociceptors, thus alleviating pain.[52]

The first published report of percutaneous bone cement injection of the proximal femur where in cadaveric osteoporotic femur,[53] subsequently, a descriptive study in 15 oncologic patients was published in 2012.[54] All patients reported pain reduction, analgesic drug consumption decreased in all patients more than 50% compared with baseline levels and was maintained throughout follow-up. Patients also improved mobility. There were no major complications, three patients presented with transient pain that improved 10 days after the procedure.

There are other reports that evaluated femoroplasty in patients with cancer.[55,56] One of the most important series, published

by Plancarte *et al*.[55] enrolled 80 patients, all had a decrease in the intensity of pain, analgesic consumption, and improved quality of life, at 7 and 30 days after the intervention. There were no complications with serious consequences reported. Only two participants experienced PMMA leakage, without clinical or functional impact.

Feng *et al*.[56] enrolled 21 patients with 23 femoroplasties with a mean follow up of 6–12 months. The pain relief efficiencies of PFP at 2 days and 6 months post-procedure were 90% and 84%, respectively. The patient scores on the Barthel Index of Activities of Daily Living 6 months post-procedure were significantly improved compared to preoperative scores. None of the patients experienced pulmonary embolism or complications of proximal femur pathological fractures during the study period.

Percutaneous bone ablation

Among the indications fot thermal ablation in bone metastases are: Painful metastases despite conventional analgesic tratment, local control in limited and/or oligometastatic disease (less than three lesions and less if 3 cm.[57] Fracture prevention and of other SREs. Ablation is usually followed by bone consolidation therapies (bone cement augmentation and or osteosynthesis) in order to reinforce the coagulated bone disease.

Over the last two decades, percutaneous image-guided procedures have emerged. Table 2 describes some of the techniques performed for the treatment of bone disease. The most frequent procedures performed are radiofrequency ablation and cryoablation.[58]

Cryoblation

Cryoablation aims destruction of cells by direct cellular and vascular injury. Usually is performed under CT, cryoablation systems use pressurized, argon and helium gases for tissue freezing and heating. The ablation zone can be visualized as a low-attenuation ice ball extending beyond the ablated zone. A 13 G cryoprobe can typically produce an ice ball measuring 5.5 cm in length and up to 3.5 cm in diameter reaching a temperature <100°C within seconds. Since there is no painful response from patient during cryoablation, the need of thermoprotective measures are mandatory, including motor and somatosensory-evoked potentials, electrostimulation and thermocouples.[58,59]

Radiofrequency-ablation

Is the most extensively and reported technique. Radiofrequency energy is applied through a closed circuit with a cathode and an anode. High-frequency alternating current induces focal ionic agitation in the target tissues around the active tips of probes with resultant rapid heat generation and lethal temperatures >60°C. Bipolar systems create an ablation zone up to 2 cm × 3 cm in size.

Table 2: Emerging techniques for metastatic bone lesions

Cryoablation
Radiofrequency ablation
Microwave ablation
Laser ablation
MRI-guided focused ultrasound

MRI: Magnetic resonance imaging

Microwave ablation

Basic microwave ablation system contains many of the same components as an RF ablation system: a generator, a power distribution system, and an interstitial applicator (antenna). Unlike RF ablation systems, microwave generators are capable of powering several antennas from the same source without the need for switching or bipolar techniques. The power distribution system may be a simple cable to transfer power directly to the antenna, or may contain components to control the phase, amplitude and duty cycle of multiple antennas. The antenna transfers energy into the tissue and could contain one of several designs, each having its own benefits and drawbacks for clinical applications. Microwaves generate heat through a process known as dielectric hysteresis: Polar molecules (e.g., water) try to continuously realign with an applied electromagnetic field that alternates polarity billions of times per second. When the molecules fail to "keep up" with the alternating field, some of the microwave energy is absorbed by the material and converted to heat.[60]

Laser ablation

Laser interstitial thermal therapy is performed using small-caliber systems with a central fiber-optic core and an outer 17 G cooling catheter. It uses infared photons to achieve lethal temperatures un an area of 1.5 cm. Laser photocoagulation is magnetic resonance imaging (MRI) compatible and it has been restricted for the treatment of benign bone tumors.

Magnetic resonance imaging-guided focused ultrasound

Is the most recent described technology in which focused ultrasound energy is delivered to the targeted tissue. Resonance imaging, is used for taget definition, treatment planning, and closed-loop control of energy deposition. Ultrasonic pulses heat up to 65–85°C generating coagulative necrosis in the tissue.[61]

Some systematic reviews have suggested that the described previous techniques achieve pain relief after 1 and 3 months, in up to 91% and 95% of patients respectively. Radiofrequency ablation combined with vertebral augmentation is effective and safe in achieving mid-term analgesia up to 6 months.[62,63]

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Conflicts of interest

There are no conflicts of interest.

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