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Bone Cancer Pain, Therapeutic Opportunities, Causes and Consequences

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Abstract : The common type of cancers which are commonly found in the human beings include cancers of breast, prostate gland, lung which involves the metastasis to bones which lead to severe life altering pain. The progression of cancer drives the pain stimulus as well. After the metastasis of cells to bone, both cancer cells and their associated stromal cells generate the pain by releasing chemical messengers like endothelins, bradykinin, proteases, prostaglandins, and tyrosine kinase activators. These chemicals are released from the cancerous cells lead to introduce a sensitization and the activation of nerve fibers cause the bone pain. Along with bone pain these chemicals also can stimulate remarkable increase in the number activity of osteoclast and bone size which ultimately results into fracture of the bone that bears tumor. The growth in tumor part also may lead to neuropathic pain by causing damage to nerve fibre as well as inducing an active and highly pathological sprouting of both sensory and sympathetic nerve fibres that innervate the bone. The anatomical organization of the sympathetic nerve fibre and sensory nerve fibre are in combination with the cellular and neurochemical organization that occurs in CNS and appears to contribute in bone pain.

Keywords: Bone cancer, Bone growth, Pain, Sensations, Osteoclast, Experimental model

Introduction

In the past decade, as per known report it was estimated 12.7 million cancer cases and 7.6 million cancer related deaths across the globe. It is predicted that in next 10 years there will be 25 million new cancer cases and 15 million deaths related to cancer. The growth rate of cancer are stable and in developed countries it is slightly decreasing, in contrast to this in the developing countries cancer growth and incidence rates are rapidly increasing due to increase in habitats like obesity, alcoholism, smoking and increased life expectancy. Due to advancement in the treatment strategies of most of the cancers, survival rates have increased so that the even patients with metastatic cancers are showing positive survival rates from years to decades beyond their initial diagnosis. The pain can be present at any point during the course of the disease, generally shows trends with increment in pain as the disease progress to advanced stages. Cancers like cancer of pancreas, cancer of neck, cancer of head the pain originates from the site of the cancer. Other common type of cancers like cancers of breast, prostate gland and lung shows metastasis that is movement of cancerous tissue to multiple bones of the body including CNS, CVS. Due the multiple sites of metastasis, this induces the significant increment in bone pain (Gorzegno G et al1999)

Now days, bone cancer pain is largely managed with an analgesic ladder that was originally promulgated by WHO in 1986. The analgesic ladder begins with NSAID, transitioning to NSAID plus a mild opiate, and finally when the pain becomes severe, NSAID plus strong opiate. Along with this 3 step ladder other adjacent therapies includes radiation therapy, antidepressant therapy, antiepileptics' therapy, and steroidal therapy which are commonly used to control cancer pain. The major goal in the cancer pain research is to develop a new therapies that are effective and with fewer side effects than the currently available therapies of analgesics. Incorporating these advances into mainstream cancer therapy has the potential to improve the quality and the life patients and of care giver as well (Thompson RC et al2000).

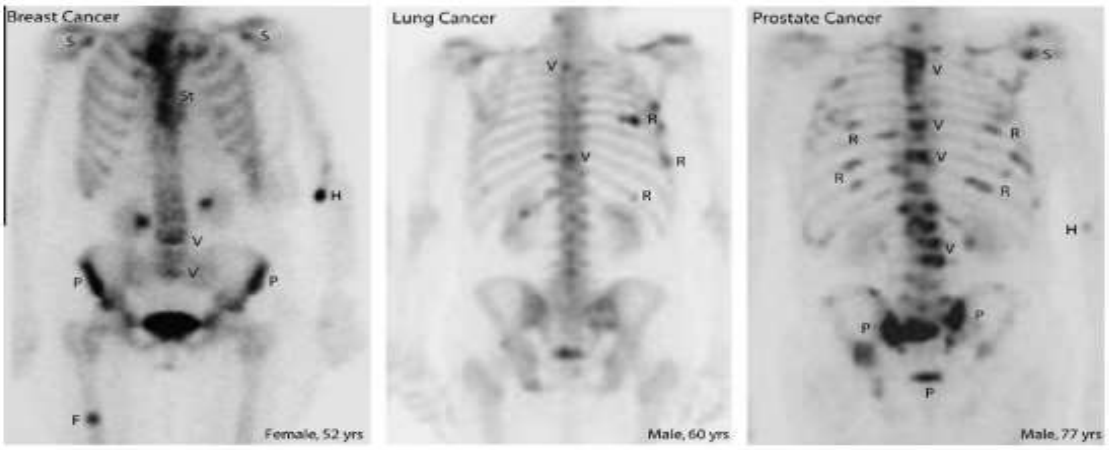

Fig. 1. Technetium-99 bone scan of patients with active breast, lung, and prostate cancers metastasized to multiple skeletal sites.

Murine model development for Bone cancer:

In early days 2 models were commonly used for study of tumor induced bone destruction. The both of the models were used in vivo. 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 the cells multiply, they grow, and they destroy the surrounding bone. This model shows the same observation that the most of common forms of solid cancers like cancers of breast, lungs, prostate gland and results in metastasis of cancer in bones, major problem with attempting to use this model to study the bone cancer pain is the differences and variations in animals to animals in the sites, size, and the extent of metastasis as well. Cancer cells that are injected into the heart also frequently metastasize into the vital organs like live, lungs and kidneys. Because of these given problems, the development of a model of bone cancer pain using inter cardiac injection is proved to be difficult at best (Mantyh et al2013).

Another type of model used to study tumor induced bone destruction involves the direct injection of cancer cells to the intra medullar space of animal. The major problem that raised in this study was that the injection site could not be plugged by using the conventional sealing and ultimately which resulted into escaping of tumor cells resulting into rapid tumor growth in nearby skin and joints, and this type of extra osseous tumor growth resulted in a large and highly variable extra skeletal tumor mass that not only interferes with the behavioral analysis but also destroys the nerves passing through these sites that are generated in the neuropathic pain state. To overcome these problems a new model was developed in which the injection hole was plugged with the amalgam that tightly bind the injection hole in the bone and prevents the escape of the tumor cells from the bone (Schwei MJ et al2000).

The unique sensory innervations of bone and joint:

The total compartments of bone marrow which includes parts like marrow, mineralized bone and overlaying periosteum are innervated by the sensory nerve fibres though the fibres shows significant variation of the density. For every 100 nerve fibres in the periosteum there are 2 in the bone marrow and 0.1 in mineralized bone. In rodents and in human there is diversity in the population of the sensory nerve fibres including thickly mylinated and thin non mylinated nerve fibres. In contrast the bone appears to be innervated by more limited repertoire of sensory nerve fibres than skin and thus it appears to be a less sensory nerve fibre. This is in accordance with the results obtained from previously studied results obtained from electron microscopy which stated that the bone is predominantly innervated by unmylinated or very thinly mylinated nerve fibres and in contrast to this thickly mylinated nerve fibres are with very rapid conduction velocities.

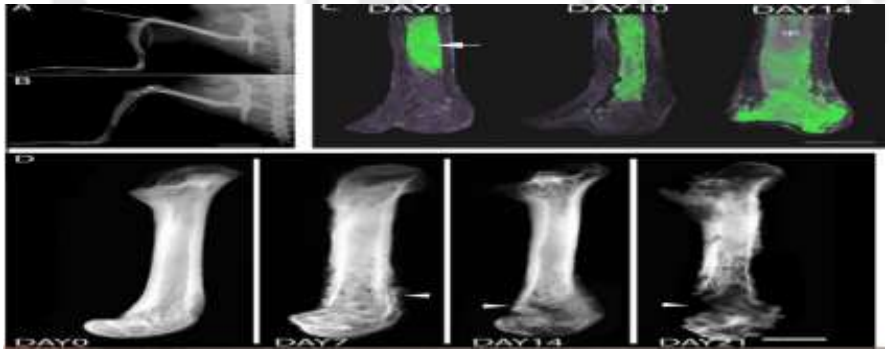

Fig. 2. Progressive destruction of mineralized bone in mice with bone cancer. (Mantyh et al2013).

Tumor induced acidosis, bone pain, and fracture:

Tumor cells of tumors such as breast, prostate, lung, renal and thyroid cancer have shown metastasis into the bone, stimulation of osteoclast activity, destruction of osteocytes, and formation of a woven mass of bone begins that can result in significant pain, decrease in the calcium level or disturbance in calcium homeostasis and skeletal fractures (Schwei MJ et al2000). Tumor cells themselves does not destroy the bone cells but rather they and their associated stromal cells express the receptor activator of nuclear factor RNKL, which binds to receptor RANK that is expressed by bone depriving cells called osteoclasts. The activation of RNKL pathway leads to the proliferation and increase in the number, size of these bone depriving, destroying osteoclasts. Osteoclast resorbs the bone by forming a highly acidic resorption pit between the osteoclast and bone that stimulates the TRPV1 channels and drives the bone cancer pain.

The widely used therapy is the use of the class of compounds called as biophosphonates that avidly binds with bone. After the binding of bisphosphonates the osteoclasts that are resorbing bone generally need to actively take up the degraded products of bone at the apical surface and transcytose these products to be released at the distal surface of the osteoclast for the disposal by exocytosis.

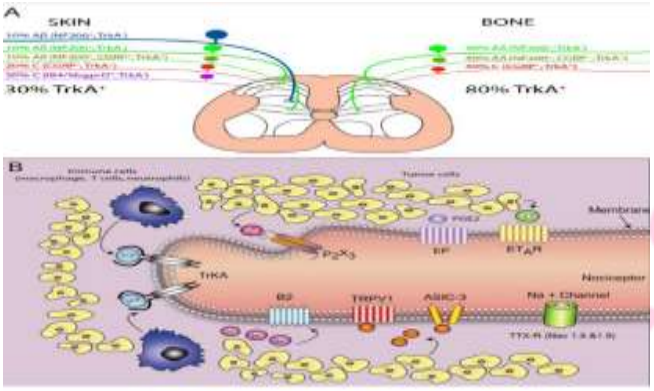

Fig. 3. The effectiveness of analgesic therapies in different types of cancer (Mantyh et al2013).

The first and most widely used therapy is the class of compounds known as bisphosphonates that avidly bind to bone. Once bound, osteoclasts that are resorbing bone generally need to actively take up the broken-down products of bone at the apical (bone facing) surface and transcytose these products to be released at the distal surface of the osteoclast for disposal by exocytosis. But if there is tightly bound bisphosphonates to bone and is reabsorbed by the bone cell endocytosis mechanism it will take bisphosphonates. One way that bisphosphonates appear to relieve bone pain is by decreasing osteoclast-induced acidosis, which in turn decreases the activation of the ion-sensing TRPV1 or ASIC3 receptors that are expressed by sensory nerve fibers.
The next option which is highly effective that it reduces the tumor induced osteoclast bone resorption in the humans as well as in animals. It acts by interfering binding of RNKL to RANK, the process that is required for the proliferation and maturation of osteoclast. In the period of 2 days of administration of the treatment therapies that interferes binding of RNKL to RANK like denosumab, osteoprotegrin (Mantyh et al2013).

There is the complete eradication of activated stage osteoclast and this marks the reduction in the plasma markers of bone resorption and a significant attenuation of the bone cancer pain in the model animal to study the pain and treatment strategies of bone cancer. In the last decade the results from multiple studies showed the these 2 treatment strategies classes reduce the osteoclast function and by same mechanism reduces pain in bone cancer and fracture induced due to the cancer, ultimately due all of these one can significantly improve functional status and quality of life of the patients suffering from bone cancer. Along with acidosis the excessive tumor induced osteoclast bone resorption destroys the bone and fractures the bone due to mechanical instability. In addition to this there is mechanical distortion of mechanical sensitive sensory nerve fibres that innervate the bone. Therapies that inhibit osteoclast-induced bone resorption not only reduce osteoclast-induced acidosis, but also maintain the mechanical strength of bone even though tumor cells are present in the bone. Both osteolytic and osteoblastic tumors induce a loss of the mechanical strength and stability of mineralized bone, so due to the significant bone remodeling mechanical stress may lead to the distortion and activation of the mechanical and sensitive nerve fibres that innervate the bone. The pain that is associated with the fracture of bone is attenuated if the bone is in stable condition and is at the normal oriented position. Because bisphosphonates and anti-RANKL therapies reduce tumor induced osteoclast bone remodeling, preserve the mechanical strength of bone, reducing bone fracture, and reduce osteoclast-induced acidosis in both animals and humans, these therapies are highly useful in managing pain caused by cancer metastasis to bone (Lipton A et al 1998).

Tumor-induced nerve injury in bone cancer:

In the cancer pain models of both prostate cancer and sarcoma and model of pancreatic cancer pain like the all other cancer type tumor cells invade the normal cells and tissue, the tumors seems to first come in contact, cause injury and then destroy the very distal processes of sensory fibres. As the tumor cells that invade the cells and tissues undergo proliferation and necrosis, they outgrow the neo vascularization that supports them and the sensory fibers go through a morphological change from a normal appearance to that of a discontinuous and fragmented appearance. This initial tumor-induced activation and then injury to the sensory nerve fibers is accompanied by an increase in ongoing and movement-evoked pain behaviors. Interestingly, there are several changes in the DRG including hypertrophy of satellite cells surrounding sensory neuron cell bodies, up regulation of ATF-3 and macrophage infiltration of the DRG that have also been described in other models of peripheral nerve injury and in other noncancerous neuropathic pain states. This study indicates the neuropathic origin of the cancer pain.

Conclusions:

The driving force behind the pain in bone cancer changes as the cancer progresses into the advanced stage. Cancer cells along with stromal cells can generate the pain the two types of pain can encompass both neuropathic and nociceptive components. The mechanism behind this pain is to be driven by stromal and tumor cells releasing elements that activates and sensitizes nociceptors, then by injury to sensory nerve fibres and then finally by the release of the growth factors that drive ectopic sprouting of nerve fibres and neuronal formation and all these can contribute for central and peripheral sensitization. The limelight into this action via which pain sensitization takes place led to the approval of the these new therapy strategies for its treatments, which includes bisphosphonates, RANKL inhibitors, and α2, d1 inhibitors and many more are in the pipeline of clinical trials. The developing therapies utilized for the treatment and to minimize the bone cancer pain has the potential to fundamentally change our ability to minimize or to block the pain of bone cancer and also boosts the quality of life and functional status of the patients suffering from metastatic bone cancer.

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