Cancer Metastasis to Bone

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The frequency with which some cancers form bone metastases had previously been related to the flow of blood from affected primary organs as well as to the richly vascularized structure of trabecular bone. There, it was thought that tumor cells trapped in the capillary beds might invade the bone and destroy bone matrix directly, creating space for the tumor to grow. It is now recognized that tumors secrete factors that stimulate bone remodeling by activating bone cells, both osteoblasts and osteoclasts. Increased bone resorption releases growth factors enmeshed in the bone matrix. This creates a vicious cycle by stimulating further tumor cell growth and greater activation of osteoclasts and osteoblasts. Sci Med 9(3):140-151, 2003.

The majority of patients dying from cancer of the breast or prostate have metastases to the skeleton. Although bone metastases are incurable, patients have mean survivals of several years, as nearly 40% of those with breast cancer bone metastases survive for 5 years. However, patients suffer serious morbidity, including fractures, spinal cord compression, and severe bone pain, as well as hypercalcemia.

In 1889, Stephen Paget observed the predilection of breast tumors to form bone metastases and proposed the “seed and soil” hypothesis: that bone provides fertile soil in which certain cancer cells (seeds) prefer to grow. We now appreciate that the affinity of breast, prostate, and several other solid tumors to grow in bone results from the special microenvironment provided by bone.

Bone is a dynamic tissue that undergoes constant remodeling in order to maintain skeletal strength. Mineralized bone matrix is a rich storehouse of growth factors, such as insulin-like growth factors, transforming growth factor-β, bone morphogenetic proteins, and others. These factors are released into the microenvironment by osteoclastic bone resorption, providing fertile soil for the growth of metastatic tumor cells.

A main effect of these local factors is to change the phenotype of tumor cells to favor their growth in bone. Tumor cells, in turn, secrete additional factors that act on bone cells, causing the skeletal responses that characterize osteolytic and osteoblastic metastases. These local interactions between tumor cells and bone form a vicious cycle, which underlies the development of skeletal metastases.

While the specific phenotypic characteristics of breast and prostate cancer cells that enable their migration and formation of distant foci remain ill-defined, the unique properties of the bone microenvironment and the local interactions between tumor and bone cells that favor metastatic development are becoming clarified. Identification of the exact nature of these tumor–bone interactions offers important information on the underlying regulatory mechanisms, which may provide potential avenues for therapeutic intervention.

Metastatic Phenotype Appears Early in Primary Tumor Cells

The genetic mechanisms of cancer metastases to specific sites have been controversial, because cancer cells mutate continuously in vivo. Metastasis is characteristic of advanced cancers and might occur only after the gradual accumulation of a necessary set of pro-metastatic mutations.

The history of this area and the continuing relevance of Paget’s seed and soil hypothesis have been summarized recently by Isaiah Fidler, a pioneer in the area. The latest experiments suggest that a
constellation of expressed genes, necessary for metastasis to bone, preexists within rare cells in the primary breast tumor. Bone-specific metastases are the consequence of selection of variants from this heterogeneous population of cells within the primary tumor, plus changes in gene expression induced by bone factors.

There are no convenient experimental animal models in which primary tumors reproducibly metastasize to bone. Many of the results achieved to date have used an animal model in which human tumor cells are inoculated into immunodeficient mice. Injection into the venous circulation most often results in tumor cell entrapment in the capillary beds of the lung or liver. However, careful tumor administration directly into the left cardiac ventricle can result in a 100% incidence of bone metastases with many tumor lines.

Osteolytic lesions are detected on radiographs as early as 3 weeks after inoculation and can be quantified by image analysis. Osteoblastic lesions may take up to 6 months to develop in nude mice, and the lesions are best quantified from histologic analyses.

**Tumor Cells Interact with Bone Cells to Produce Metastases**

Cancer cells in very advanced metastases may lay down or destroy bone matrix directly, but in most cases of bone metastases, the effects of tumor cells on the skeleton are

**Angiogenesis** in primary tumors allows isolated cancer cells to enter the circulation. These cells adhere to blood vessel walls and extravasate from the capillary bed into bone, where they proliferate in this fertile microenvironment. Tumor cells secrete proteolytic enzymes that disrupt the basement membrane and enhance tumor invasion. Multiple micro-metastases may be present throughout the bone.
Typical digital radiographs showing osteolytic (left) and osteoblastic metastases (right) in nude mice injected with a human prostate cancer cell line.

mediated by bone cells. The main cell types in bone are osteoblasts, osteoclasts, endothelial cells, and marrow elements, including stem cells with differentiation potential. Of these, osteoblasts and osteoclasts are the principal cell types involved in tumor metastases.

Osteolytic metastases predominate in breast cancer. Their growth is usually indolent, and progression from microscopic lesion to diagnosable tumor is likely a long process. The initial steps in the development of osteolytic lesions have not been examined in depth in animal models. In later disease, tumor cells are known to secrete proteolytic enzymes and acid, which can destroy bone matrix in vitro. During the establishment of metastases, however, histologic analysis and scanning electron microscopy indicate that bone destruction is mediated by osteoclasts rather than by tumor cells.

Histologic sections of osteolytic (left) and osteoblastic metastases (right) in mice. In the osteolytic metastasis, tumor cells have replaced normal marrow and destroyed trabecular and cortical bone. In the osteoblastic metastasis, the marrow cavity has been filled with excessive trabecular bone surrounded by tumor cells.
Osteoclasts are large multinucleated cells, of the monocyte-macrophage hematopoietic lineage, that adhere tightly to the bone surface and secrete acid and hydrolytic enzymes onto it. Osteoclasts are a rare cell type in bone, and in recent years dramatic progress has been made in understanding the molecular regulation of their formation and activity.

Osteoblastic metastases, in contrast, are characteristic of prostate cancer but also occur in 15% of breast cancer bone metastases. Tumor-induced lesions show disorganized new bone formation and are accompanied by increased bone resorption. This activity is mediated primarily by osteoblasts, which share a common origin with fibroblasts and with fat and muscle cells (stromal stem cells).

Biochemical markers of bone resorption are significantly increased in patients with osteoblastic metastases. The increases are frequently greater than those seen in patients with osteolytic disease. A number of candidate factors made by tumor cells could stimulate osteoblasts, but progress in testing such candidates has lagged until recently.

Complicating this picture is the intimate relationship between osteoblasts and osteoclasts. Osteoblasts control the formation, activity, and survival of osteoclasts. They do this by expressing on their surface a molecule called RANK ligand, which binds to a receptor on the osteoclast. Conversely, osteoblasts preferentially fill in resorption pits created by osteoclasts.

The mechanisms for this coupling are unknown. When skeletal metastases are examined histologically, bone cells are observed at the interface between tumor cells and mineralized matrix. Osteolytic metastases are characterized by an abundance of osteoclasts resorbing bone. Osteoblastic metastases show plump, metabolically active osteoblasts covering the surface of bone with a layer of incompletely mineralized osteoid.

In normal bone remodeling, old bone is rapidly destroyed by large, multinucleated osteoclasts with short lifespans (2 weeks). The pits left by osteoclastic resorption are invaded by long-lived (2 months) osteoblasts, which gradually fill the pits. Osteoblasts secrete collagenous matrix and vesicles containing calcium phosphate to form osteoid, which matures into bone. Slight imbalances in the ratio of osteoclast to osteoblast activities can result in a net loss or gain of bone.

Tumor-Derived PTHrP Induces Bone Resorption

Parathyroid hormone-related protein is a widely expressed factor that shares sequence homology with parathyroid hormone. It was originally identified as a systemic causal factor of humoral hypercalcemia of malignancy. The widespread expression of PTHrP by breast cancer cells, particularly in bone metastases, led us to test if PTHrP also played a causal role in osteolytic metastases.

In a mouse model, treatment with a neutralizing antibody against PTHrP dramatically decreased bone metastases caused by a breast cancer cell line that secretes low concentrations of PTHrP. Tumor burden also was decreased, and survival was increased.

When this same breast cancer cell line was challenged in vitro with bone-derived growth factors (TGF-β, IGF-1 and 2, FGF-1 and 2, BMPs, PDGF), only TGF-β stimulated tumor production of PTHrP. After the breast cancer cells were engineered to be resistant to TGF-β, bone metastases and tumor burden were again reduced.

PTHrP-neutralizing antibody has been humanized and is in clinical trials, while reagents to inhibit TGF-β signaling are in preclinical testing.

Tumor cells secrete PTHrP and other osteolytic factors, which stimulate multinucleated osteoclasts to resorb bone. This resorption releases factors from the bone matrix (in particular TGF-β), which in turn change the phenotype of the tumor cells, further increasing PTHrP production. This creates a vicious osteolytic cycle between tumor cells and bone.

**Tumor Cells Secrete Osteolytic and Osteoblastic Factors**

The most prominent cause of bone destruction in metastases is parathyroid hormone-related peptide (PTHrP), which stimulates osteoclastic bone resorption. This factor is immunologically distinct from PTH but shares a common receptor and similar biological effects. It is secreted by many cancer types, and when systemically elevated, PTHrP is responsible for humoral hypercalcemia of malignancy.

At lower levels, PTHrP can still cause bone destruction. Breast cancer cells that secrete PTHrP in concentrations insufficient to induce hypercalcemia still cause extensive osteolytic bone destruction in nude mice.

In experiments in mice examining the role of PTHrP in osteolytic metastases, it was shown that bone lesions and tumor burden can be significantly decreased, and survival increased, by treatment with PTHrP-neutralizing antibody, which breaks the vicious cycle between tumor cells and bone.

PTHRP cannot be the only factor responsible for bone metastases, and breast cancer cells also secrete other factors that can increase osteolytic bone metastases by increasing osteoclast number, activity, and survival. These factors include interleukins 6, 8, and 11, macrophage colony-stimulating factor (M-CSF), and vascular endothelial growth factor (VEGF, which stimulates bone cells as well as angiogenesis).

Tumor production of most of these factors is increased by TGF-β, and van der Pluijm and colleagues have found several of them to be increased in metastases to bone versus those to soft tissue sites.

Yibin Kang and his colleagues compared less- and more-metastatic variants of a breast cancer cell line by gene expression profiling. They identified five mRNAs whose expression strongly correlated with increased bone metastasis. The authors found that the pro-metastatic gene set was coordinately increased in cells that existed in the original cell population, rather than arising in later divisions.

It has been controversial whether metastases arise from cells (subclones) existing from an early stage within the main tumor or from mutations arising late during tumor progression. The data of Kang and colleagues strongly support the former model.
The authors attempted to convert low-metastatic breast cancer cell line clones into ones highly metastatic to bone by overexpressing each of five individual genes. These encoded IL-11, matrix metalloproteinase-1 (MMP-1), osteopontin, connective tissue growth factor (CTGF), and CXCR-4.

Conversion to an aggressive osteotropic phenotype required cotransduction of combinations of four of the five factors. The results strongly support a multifactorial mechanism underlying organ-specific metastases.

MMP-1 is an interstitial collagenase made by osteoblasts. It cleaves collagen in bone at a site resistant to osteoclastic action and may be rate-limiting in normal bone resorption.

Osteopontin, a protein secreted by osteoblasts and tumor cells, plays a complex role in metastasis, including modulation of antitumor immune responses. CTGF recently has been discovered to be a potent osteoblast-stimulatory factor, as well as being expressed by tumor cells.

CXCR-4 is the receptor for a chemokine molecule, SDF-1. It functions to attract breast cancer cells to specific metastatic sites including, but not limited to, bone. Antagonists of CXCR-4 (which also is a co-receptor for HIV) have been developed and could be clinically useful as antimetastatic agents.

Among the osteoblastic factors secreted by tumor cells is endothelin-1 (ET-1), a 21-amino-acid vasoactive peptide, that is a potent stimulator of new bone formation. ET-1 has been shown to cause osteoblastic metastases in a preclinical model developed by Juan Juan Yin and Theresa Guise.

In their model, a selective antagonist of the endothelin A receptor (Atrasentan, ABT-627) blocked bone metastases and decreased tumor burden. The same orally active antagonist is in clinical trials in men with advanced metastatic prostate cancer.

The vicious cycle model predicts that osteoblasts, osteoclasts, and tumor cells cooperate to cause the pathology of bone metastases. The endothelin receptor antagonist blocked the activation of osteoblasts by tumor-produced ET-1. It also decreased osteoclastic bone resorption, as indicated by a reduction in markers of resorption seen in the patient trials. This reduction may be an indirect effect of the endothelin A receptor antagonist to reduce osteoblast activity and the associated increase in bone remodeling.

**Tumor cells secrete** osteoblast-stimulatory factors, such as endothelin-1 (ET-1), which cause osteoblast proliferation and maturation. Osteoblasts lay down new bone on the surfaces of existing bone and also synthesize growth factors. These are incorporated into mineralized bone matrix and also released into the local microenvironment, where they can act back on the tumor cells.

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**Tumor and bone cells** interact in a vicious cycle. In the osteolytic cycle, tumor cells stimulate osteoclastic bone resorption, which releases factors such as TGF-β, which in turn stimulate tumor cells to produce PTHrP.

In the osteoblastic cycle, tumor cells release osteoblast-stimulatory factors such as endothelin-1 (ET-1). The stimulated osteoblasts synthesize new bone and release undefined factors into the bone microenvironment, which in turn stimulate the tumor cells.

Clinically approved bisphosphonate drugs (inhibitors of osteoclasts rather than osteoblasts) decrease skeletal-related events in patients with prostate cancer bone metastases. These observations support a role for both osteoblasts and osteoclasts in the vicious cycle of bone metastasis in humans. It is notable that these therapies against bone metastases target to bone cells rather than tumor cells, which are the usual targets of conventional chemotherapy.

Other factors responsible for osteoblastic metastases remain to be identified. Such factors should meet two criteria: (1) ability to stimulate new bone formation, and (2) expression by cancer cells.

The bone morphogenetic proteins are obvious candidates, but a causal role in bone metastases has not yet been demonstrated. Connective tissue growth factor (CTGF) was identified in the experiments of Kang and colleagues, where it was shown to stimulate osteoblasts. Adrenomedullin is a 52-amino-acid vasoactive peptide with potent bone-stimulatory actions that is secreted by many cancers; recently we have found that it increases bone metastases in animal models of lung adenocarcinoma and androgen-independent prostate cancer.

**Tumor and Bone Cells Interact in a Vicious Cycle**

Animal experiments have established that bone metastases involve a vicious cycle between tumor cells and the skeleton. Four contributors fuel the cycle: tumor cells, bone-forming osteoblasts, bone-destroying osteoclasts, and organic bone matrix. Osteoclast formation and activity are regulated by the osteoblast, adding complexity to the vicious cycle.

The mineralized matrix of bone is a storehouse of growth factors, such as insulin-like and transforming growth factors. These factors are synthesized by osteoblasts and released by osteoclasts. The factors reach high local concentrations in the bone microenvironment and can act on tumor cells to encourage metastatic growth.

Cancer cells secrete many factors that act on bone cells. At sites of metastases, tumor cells secrete osteoblast-stimulatory factors, such as ET-1, and osteolytic factors, such as PTHrP.

Therapies targeting the vicious cycle can decrease metastases by lowering the concentrations of growth factors in bone. The most established such therapy is the bisphosphonate class of antiresorptive drugs, which home to bone with...
The regulation of osteoclasts by osteoblasts has been recognized for over 15 years, but its molecular basis has been understood only recently. Cells of the osteoblast lineage express the RANK (receptor activator of NF-κB) ligand, which in combination with M-CSF, induces the differentiation of osteoclasts from hematopoietic precursors.

Many osteolytic factors, rather than acting directly on osteoclasts to stimulate bone resorption, act indirectly via osteoblasts and RANK ligand. This has been shown for organic mediators (e.g., prostaglandin E₂, 1,25-dihydroxyvitamin D₃) and protein factors (PTH, PTHrP, IL-6, IL-11), which induce expression of RANK ligand on osteoblasts. M-CSF and VEGF serve as cofactors required for the differentiation of hematopoietic precursors into active osteoclasts.

RANK ligand is a member of the TNF superfamily and is expressed on the cell surface of osteoblasts. Opposing its actions is osteoprotegerin (OPG), a soluble member of the TNF receptor superfamily that is secreted by osteoblasts. Overexpression of OPG in mice has been shown to result in osteopetrosis, whereas mice deficient in OPG are osteoporotic.

While osteoclastogenic molecules stimulate expression of RANK ligand, they also blunt production of OPG. Osteoblastic cells regulate osteoclast formation and activity through the ratio of these two opposing factors.

RNA abundances were determined by species-specific reverse-transcriptase PCR. PTHrP, VEGF, and M-CSF were increased specifically in bone as compared to nonbone sites of human breast cancer metastases.

Insulin-like growth factors and TGF-β are the most abundant bioactive proteins in bone matrix, followed by lower concentrations of bone morphogenetic proteins, fibroblast growth factors, and platelet-derived growth factor. Of these, only TGF-β has shown a direct role in stimulating tumor cells.

TGF-β is growth inhibitory in the early stages of tumorigenesis. Advanced cancers lose growth inhibition but retain TGF-β regulation of metastasis-promoting genes (e.g., CTGF, IL-11, PTHrP). In a model of breast cancer metastasis to bone, experiments carried out by Juan Juan Yin and Sanna Käkönen in collaboration with Joan Massagué showed that tumor expression of PTHrP is the major target of TGF-β and that TGF-β in turn is the most important regulator of PTHrP.

Recent preclinical experiments suggest that extracellular TGF-β and its intracellular signaling may be practical targets for antimetastatic therapies. Osteoclastic bone resorption specifically activates
Tumor stimulation of osteoblasts can increase both new bone formation and resorption. Tumor products, such as adrenomedullin and ET-1, stimulate osteoblast proliferation. Mature osteoblasts synthesize growth factors, which are in turn incorporated into bone.

Immature osteoblasts respond to osteolytic cytokines (e.g., PTHrP, IL-11) by expressing RANK ligand. RANK ligand stimulates bone resorption by osteoclasts, which in turn release growth factors from mineralized matrix that enrich the local microenvironment. Growth factors stimulate tumor cells. Osteoblasts lose RANK ligand expression during maturation.

The balance of osteoblast proliferation versus maturation, plus tumor production of factors such as PTHrP, determines whether bone metastases are osteoblastic or osteolytic. Both are common in breast cancer, and both responses may occur at the same site.

TGF-$\beta$ from its stored form in bone matrix, so this step may be another point of action for bisphosphonate antiresorptive treatment.

**Mixed Osteoblastic and Osteolytic Signals Stimulate Greater Bone Resorption**

Mixed osteolytic/osteoblastic metastases are common in both breast and prostate cancers. The effect of combined expression of osteolytic and osteoblastic factors on bone has not been studied, so the net response of bone at the metastatic site is unpredictable.

As noted, osteolytic factors such as PTHrP and IL-11 act on osteoblasts to increase expression of RANK ligand. To test the effects of osteoblastic stimulation on tumors, we introduced ET-1 into a PTHrP-secreting breast cancer cell line. Instead of converting the bone response from osteolytic to osteoblastic, ET-1 increased bone destruction.

We suspect that factors like ET-1 stimulate osteoblast proliferation, increasing the population of early osteoblasts. The enlarged pool of early osteoblasts in turn responds to osteolytic factors by increased expression of RANK ligand.

Another question has been the role of PTHrP in osteoblastic metastases, especially those due to prostate cancers, which nearly always express PTHrP. A partial explanation was provided by the discovery that prostate-specific antigen (PSA) is a protease that cleaves PTHrP after amino acid 23. The resulting fragment fails to activate the classical PTHrP receptor, but this is not the end of the story.

In experiments, the inactive fragment PTHrP 1–16 stimulated cardiomyocytes by binding to the endothelin A receptor. Binding was attributed to a 4-amino-acid homology between the two peptides.

We have recently extended these observations to bone. PTHrP 1–23 potently stimulated osteoblast activity and new bone formation by activating the endothelin A receptor. The results suggest that PSA proteolysis of PTHrP, rather than inactivating PTHrP, converts the protein from an osteolytic factor to an osteoblastic one.

**Tumor–Bone Interactions Are Targets for Antimetastatic Therapy**

The “vicious cycle” model provides a molecular rationale for the tropism of certain tumors for bone. The specific molecular interactions that drive the vicious cycle cause the
morbidity and mortality associated with skeletal metastases. These same interactions also offer novel targets for antimetastatic therapy.

The bisphosphonates are a class of drugs that share a simple chemical structure \([\text{O}_3\text{P}–\text{C}–\text{PO}_3]\), which mimics pyrophosphate \([\text{O}_3\text{P}–\text{O}–\text{PO}_3]\). The bisphosphonate backbone provides two functions: resistance to hydrolysis (unlike pyrophosphate itself) and a high affinity for bone mineral.

Most bisphosphonates in clinical use share the basic structure \(\text{O}_3\text{P}–\text{C(OH)}(\text{R})–\text{PO}_3\). The hydroxyl group increases the affinity for bone, and \(\text{R}\) contains nitrogen in the amino bisphosphonate class.

Amino bisphosphonates, such as pamidronate, ibandronate, and zoledronic acid, inhibit farnesyl pyrophosphate synthase in the HMG CoA reductase/mevalonate pathway. This inhibition decreases the prenylation of GTP-binding proteins such as Rho, resulting in osteoclast apoptosis.

A key to the actions of bisphosphonates is their affinity for bone. Once bound to mineralized matrix, they can persist for years and are released at locally high concentrations at sites of active bone remodeling. Affinity for bone mineral is also the basis for bisphosphonate-radionuclide conjugates as bone-scanning agents used in the diagnosis of prostate cancer bone metastases.

Bisphosphonates are readily taken up by cells, such as osteoclasts. The net effect on osteoclasts is cell death through activation of apoptosis. Bisphosphonates may have many, low-specificity biochemical actions, but these are limited by the cellular concentrations achieved in vivo.

Many effects of bisphosphonates have been reported in vitro, often at high concentrations of drug. These include effects on the tumor cell, local angiogenesis, and osteoblasts, but the importance of such actions in the clinic remains highly controversial.

It also may be possible to target standard inhibitory agents to bone by coupling them to the bisphosphonate backbone. Demonstrations of this approach have been published.

Numerous bisphosphonates are in clinical use for diseases associated with increased osteoclastic bone resorption. Pamidronate and zoledronic acid are approved for breast and prostate cancer bone metastases and multiple myeloma bone disease. However, they have not been shown to cause regression of established bone lesions.

**Bisphosphonates** have a characteristic P-C-P moiety that leads to their selective accumulation in bone. There, bisphosphonates released by osteoclastic bone resorption are taken up by osteoclasts, causing a loss of resorptive capacity. It is believed that bisphosphonates act by inhibiting ATP-dependent intracellular enzymes or by disrupting small GTPases via the mevalonate pathway, leading to osteoclast apoptosis.

Bisphosphonate also may affect metastatic tumor cells via two mechanisms. First, bisphosphonate-induced osteoclast apoptosis causes a loss of growth factors, which results in reduced stimulation to the tumor cell. Also, bisphosphonates released from bone may be taken up directly by tumor cells, where they disrupt the mevalonate pathway and lead to tumor cell death.
A modified recombinant version of osteoprotegerin inhibits osteoclast formation, activity, and survival. In an animal model, injected osteoprotegerin decreased osteolytic destruction and tumor burden in bone, without affecting metastases to soft-tissue sites. In other models of cancer bone metastasis, osteoprotegerin treatment effectively decreased bone pain.

Recombinant osteoprotegerin has entered initial clinical trials, but it is unclear whether it will prove superior to the widely used and more convenient bisphosphonate antiresorptive agents. Other drugs targeting RANK ligand are also under development.

The PTHrP neutralizing antibody, which was tested against osteolytic metastases in preclinical models, has been humanized and is in clinical trials. In addition, a number of newer targets in osteolytic metastases are being tested, including the TGF-β signaling pathway in tumor cells and the calcium-sensing receptor, since extracellular calcium is increased by bone resorption and increases PTHrP production.

Small molecule inhibitors of intracellular signaling in either bone or cancer cells have not been reported to be effective against bone metastases, though the range of testable targets is very wide.

A recent study was designed to inhibit the gene promoter responsible for PTHrP transcription in tumor cells. The investigators used a PTHrP promoter-luciferase reporter in a high-throughput screen of small molecules and identified two related molecules as effective inhibitors of PTHrP transcription: 6-thioguanine and 6-thioguanosine.

These agents have been used for over a quarter century against leukemias and several inflammatory disorders. When tested in animal models of humoral hypercalcemia of malignancy and against breast cancer bone metastases, both were effective in reducing osteoclastic bone resorption, which makes bone a less favorable environment for tumor growth.

The only drug tested to date that targets the osteoblast is the endothelin A receptor antagonist atresanten, the results of which were discussed earlier.
Bone Loss Can Also Be Related to Cancer Therapy

Bone metastases are not the only cause of skeletal morbidity in cancer patients. Patients with prostate and breast cancer are often sex-steroid deficient due to their treatment, resulting in increased osteoclastic bone resorption, bone loss, and risk of fracture. Sex steroids have complex effects on both bone and tumor cells.

Patients with advanced prostate cancer are routinely treated by androgen ablation. As in females, hypogonadism also causes osteoporosis in men. Bisphosphonate treatment can prevent bone loss in this situation.

Women who have had breast cancer are at increased risk for osteoporosis. They often have early menopause due to chemotherapy-induced ovarian failure or oophorectomy. Chemotherapy also may have a direct adverse effect on bone mineral density, and osteoclastic activity may be increased by tumor.

Tamoxifen treatment causes significant bone loss in premenopausal women, while preventing it in postmenopausal women. Women with breast cancer show an incidence of vertebral fracture that is nearly 5 times greater than that in normal women and 20 times higher than that in women with soft-tissue metastases. Selective estrogen-receptor modulators (SERMS), such as raloxifene, may play an important role in treating breast cancer without causing bone loss.

Active metabolites of vitamin D can increase RANK ligand and bone resorption. At the same time, vitamin D metabolites have powerful antitumor effects. As is the case with other steroid derivatives, the use of selective receptor-modulating vitamin D analogues could be effective against cancer cells, while sparing bone.

Aromatase inhibitors, now gaining rapid acceptance as primary therapy for breast cancer, cause significant bone loss and increased fracture risk.

There are speculations and preclinical data that the increased bone resorption in breast and prostate cancer due to sex-steroid deficiency may actually enhance bone metastases. Since increased bone resorption accelerates the vicious cycle of bone metastasis, treatments that increase resorption could stimulate the vicious cycle. If this idea is correct, such undesirable side effects of cancer treatment could be decreased with anti-resorptive adjuvant therapy.

Future directions include identification of novel osteolytic and osteoblastic factors. Many of the known ones, such as IL-8, IL-11, CTGF, adenomedullin, and CXCR-4, require more testing to determine if they are useful targets for therapy. Bone-derived insulin-like growth factors need to be tested for their contributions to bone metastasis.

Also, the relationship between bone metastases and secondary effects of cancer remain to be studied. The association between bone metastases and angiogenesis needs to be clarified, as do the mechanisms of cancer-related bone pain. Bone metastases probably release unknown factors into the circulation that stimulate wasting of skeletal muscle, which in turn may contribute to mortality.

Tumor-bone interactions, and the secreted factors that mediate them, offer targets for future therapeutic interventions to alleviate or perhaps prevent bone metastases.

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