

Mechanisms and Treatment for Bone Metastases

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Abstract

Alterations in bone architecture and mineral metabolism are common complications of malignancy. Cancers such as breast, prostate, and lung can affect the skeleton either indirectly through the elaboration of factors that act to disrupt normal calcium homeostasis at the level of the kidney and bone; or directly via secondary spread of tumor to bone. Although the pathophysiology of these skeletal complications is diverse, it is clear that the osteoclast and osteoblast are not just bystanders but are active participants in the development and progression of hypercalcemia and bone metastasis. Our understanding of the molecular mechanisms of metastasis leading to tumor cell escape, homing, adhesion, and secondary growth in a hospitable environment are evolving. Treatment modalities aimed at not only reducing tumor burden but altering the skeletal response to tumor have shown benefit. Newer generation bisphosphonates are quite effective in controlling hypercalcemia of malignancy and have been shown to delay progression of skeletal metastases. Clearly, cancer-associated bone morbidity remains a major public health problem. To improve therapy and prevention it is important to understand the pathophysiology of the effects of cancer on bone. This review will detail scientific advances regarding this area.

Introduction

The skeleton invasion of malignant cells from distant primary sites often occurs during the final stages of cancer. Metastatic bone disease is a dreaded complication that can lead to significant bone pain, pathologic fractures, and spinal cord compression. The development of bone metastases indicates that cure is unlikely and management of symptoms becomes a focus. Each of the 3 most common human neoplasms—breast, prostate, and lung—is strongly associated with skeletal morbidity. In the United States alone, it is estimated that in 2003 there will be 212,600 new cases of breast cancer and 220,900 new cases of prostate cancer. These will cause 40,200 and 28,900 deaths, respectively. At the same time the combined number of lung cancers for males and females is estimated to be 171,900 with 157,200 deaths.¹ The majority of patients dying from these cancers will have bony involvement either through metastatic spread or as a result of systemic tumor-produced factors. Because bone metastasis is such an important complication of some of the most common tumors, understanding the cellular events involved and devising therapeutic strategies to prevent new metastasis and inhibit continued growth of established metastases is a very important therapeutic goal for cancer management. This review details scientific advances in mechanisms, diagnosis, and treatment of solid tumor metastases to bone.

Molecular Mechanisms

Metastatic bone disease is typically classified as osteolytic or osteoblastic but most cancers lie within a spectrum of these extremes. Osteolytic metastases are much more common, are usually destructive, and are much more likely to be associated with pathologic fracture and hypercalcemia. It is clear that there are important properties of both the tumor cell (the seed) and the skeleton (the soil) that determine the likelihood that any particular tumor will metastasize to bone. The mechanism by which a solitary tumor is able to escape and invade other distant structures is beginning to be understood. Once tumor cells enter the circulation, they traverse vascular organs, including the red bone marrow, where they migrate through wide-channeled sinusoids to the endosteal bone surface. The process of metastasis can be divided into 4 stages: escape from the primary site, homing to a particular organ or tissue, adhesion to and invasion of that structure, and propagation in a hospitable environment. The propensity of tumors to spread to preferred sites suggests specific

Keywords

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molecular interactions of the tumor cells with the environment at the site of metastases.

General Mechanisms

A comprehensive investigation to identify gene products that enhance breast cancer metastatic potential demonstrated that patients who develop metastases have unique gene expression profile signatures and are predictive of aggressive disease.² The overexpressed gene products belonged to families that control cell cycling, angiogenesis, and invasion. A similar study using gene expression profiling was reported but focused on gene products that have a specific role in bone metastasis. The human breast cancer cell line MDA-MB-231 forms osteolytic bone disease when introduced into athymic mice via intracardiac inoculation.³ Subpopulations of MDA-MB-231 that have a greater osteolytic potential than the parental cell line were isolated by serial passage and gene expression profile comparison to the parental cell line was performed.⁴ Eleven genes were identified that have a greater than 4-fold expression pattern in the highly bone-metastatic line. Four of these gene products—interleukin-11 (IL-11), connective tissue growth factor (CTGF), the chemokine receptor CXCR4, and matrix metalloproteinase 1 (MMP-1)—were analyzed further. Overexpression of not a single gene but a combination of 2 or more in parental MDA-MB-231 enhanced *in vivo* osteolytic capacity. Thus, these genes that have different function, such as chemotaxis, invasion, and osteolysis, cooperate to produce a full bone-metastasis potential. None of these genes were represented in the report by van't Veer et al² in a gene expression study of primary tumors implying that breast cancer cells are capable of developing osteotropic potential rather than possessing inherent ability to metastasize to bone.

Before establishing a metastatic lesion in bone or any tissue, tumor cells must first adhere to extracellular matrix components and other cells. The predilection of certain tumors to metastasize to specific characteristic tissues is likely to be determined by ligand-receptor interactions between specific tumor cell type and target site.⁵ The stromal cell-derived factor-1a (SDF1a, also known as CXCL12) is a factor that is present in tissues that represent common sites of metastasis, including bone marrow.⁶ This ligand has an affinity for the chemokine receptor CXCR4, which is highly expressed in breast and prostate cancer cells. Blockade of this interaction *in vitro* inhibits migration of prostate cancer cells through bone marrow endothelial cells.⁷ Adhesion molecule, $\alpha_v\beta_3$ integrin, binds the RGD peptide sequence that is found on a variety of extracellular matrix proteins—including osteopontin, vitronectin, and bone sialoprotein—and may also be important in homing and possibly invasion of tumor cells into the bone endosteum.^{8,9} The matrix metalloproteinases (MMPs) participate in the progression of cancer metastases not only by the degradation of matrix leading to invasion but alteration of signaling molecules affecting tumor growth and migration through the cleavage of tethered signaling molecules such as insulin-like growth factor binding protein 1, E-cadherin, fibroblast growth factor receptor 1, and pro-transforming growth factor β .¹⁰ The expression of MMPs has

been found to be increased in most cancer types, including breast and prostate,^{11,12} and high levels have been associated with poor prognosis.^{13,14}

Mediators of Osteolytic Bone Destruction

Significant progress has been made in the last several years elucidating the paracrine molecular interactions of breast cancer metastases with the local bone environment. Parathyroid hormone-related protein (PTHrP) is produced in excessive amounts, particularly in patients with metastatic breast cancer, but produced relatively specifically in the bone microenvironment.¹⁵⁻¹⁷ The increased local PTHrP concentration drives the receptor activator of nuclear factor B ligand (RANKL) expression and inhibits osteoprotegerin (OPG) secretion from osteoblasts and stromal cells, thereby activating osteoclastogenesis via the receptor activator of nuclear factor B (RANK) located on osteoclast precursors.¹⁸ This production of PTHrP in the bone microenvironment is due to bone-derived transforming growth factor β (TGF β), which is released in active form as a consequence of bone resorption. Thus the vicious cycle begins: tumor cell production of PTHrP stimulates osteoclastic bone resorption and release of more TGF β , which in turn stimulates more tumor-produced PTHrP.

Tumor cells also produce a number of other important factors that lead to osteolysis such as IL-8, IL-6, IL-11, and vascular endothelial growth factor (VEGF).¹⁹ IL-6, IL-11, and VEGF are not only secreted by osteolytic breast cancer cell lines, but their production is increased in response to TGF β stimulation. Importantly, these factors can potentiate the effects of PTHrP on osteoclastic bone resorption.^{20,21} Bone-derived factors besides TGF β also contribute to the vicious cycle. The insulin-like growth factors are released into the local bone environment during osteolysis and likely also have a role in the proliferation of bone metastases.^{22,23} Extracellular calcium is also released as a consequence of osteoclastic bone resorption and stimulates tumor PTHrP production,^{24,25} the effect of which is enhanced in the presence of TGF β .

Mediators of Osteoblastic Metastases

Prostate cancer has a predilection to metastasize to the axial skeleton, where these lesions are typically osteoblastic. A similar vicious cycle likely occurs with prostate cancer bone metastases, whereby factors secreted from cancer cells stimulate osteoblasts to secrete tumor mitogenic factors. In recent studies, tumor-produced endothelin-1 (ET-1) has recently been implicated in the pathogenesis of osteoblastic metastases.²⁶ The human breast cancer cell line ZR-75-1 secretes ET-1 and produces osteoblastic bone lesions when inoculated through the left cardiac ventricle of nude mice. ET-1 was also shown to stimulate osteoblast activity and new bone formation in neonatal mouse calvariae organ culture model; this effect was blocked by the endothelin A (ETA) receptor antagonist ABT-627, atrasentan. Furthermore, oral administration of ABT-627 blocked the development and progression of osteoblastic bone metastases due to ZR-75-1. In fact, the ETA antagonist atrasentan is in clinical trials for men with advanced prostate cancer and early results show benefit.²⁷

Other factors responsible for osteoblastic metastases remain to be identified. Such factors need to meet 2 initial criteria: ability to stimulate osteoblastic new bone formation, and expression by cancer cells. The bone morphogenetic proteins (BMPs) are obvious candidates, but a causal role in bone metastases has not been demonstrated. CTGF, identified in the experiments of Kang et al⁴ is another factor that stimulates osteoblasts.²⁸ Adrenomedullin is a 52-amino acid vasoactive peptide with potent bone-stimulatory actions.²⁹ It is made by many cancers,³⁰ and we have recent data that it increases bone metastases in vivo.

Effects of Bone on Tumor Cells

Preclinical animal models have established that bone metastases involve a vicious cycle between tumor cells and the skeleton. Four contributors fuel the cycle: the tumor cells, bone-forming osteoblasts, bone-destroying osteoclasts, and organic bone matrix. Osteoclast formation and activity is regulated by the osteoblast, adding complexity to the vicious cycle. The mineralized matrix of bone is a vast storehouse of growth factors, such as insulin-like and transforming growth factors. These 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 probably secrete osteoblast-stimulatory and osteolytic factors, such as parathyroid hormone-related protein, which stimulate bone resorption. Therapies targeting the vicious cycle can decrease metastases by lowering the concentrations of growth factors in bone. The most established, the bisphosphonate class of antiresorptive drugs, which home to bone with high affinity and inhibit osteoclastic bone resorption, provides such therapy.

The effects of bone-derived factors on tumor cells remain understudied. Van der Pluijm et al³¹ elegantly demonstrated that several mRNAs are increased in bone versus nonbone sites of human breast cancer metastases in nude mice. RNA abundances were determined by species-specific RT-PCR. PTHrP, VEGF, and M-CSF were increased specifically in bone, while several mouse markers of host angiogenesis were similarly increased. These experiments did not identify the factor or factors responsible for the bone-specific mRNA induction. Insulin-like growth factors (IGFs) I and II are the most abundant factors in bone matrix, followed by TGF β , after which are lower concentrations of BMPs, fibroblast growth factors -1 and -2, and platelet-derived growth factor. Of these, only TGF β has been shown to play 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 (such as CTGF and IL-11, identified by Kang et al,⁴ and PTHrP).³² In the MDA-MB-231 model of breast cancer metastasis to bone, detailed experiments showed that tumor cell expression of PTHrP is the major target of TGF β and that TGF β is the most important regulator of PTHrP. These experiments also showed that dual pathways in the tumor cells, through

p38 MAP kinase and through the Smad proteins, transmit TGF β signaling to the nucleus. Osteoclastic bone resorption specifically activates TGF β from its stored form in bone matrix. This step may be another point at which bisphosphonate antiresorptive treatment exerts its specificity.

Clinical Features of Bone Metastases

Bone pain is a frequent cancer-related complication with the spine being a common location of metastasis. As this is often an initial symptom, distinguishing metastatic bone disease from common causes of back pain such as disc disease and muscle strain can be difficult. However, there are warning signs that should alert the physician that the patient's discomfort could be due to a serious condition. Progressive pain in an older individual or a patient with a history of cancer warrants further investigation. One study evaluated the etiology of back pain in 1,975 patients in a primary care setting and discovered that 0.66% of patients had a malignancy.³³ Other worrisome signs and symptoms include age greater than 50, weight loss, no relief with bed rest, and duration greater than 1 month.³³ A patient that is found to have lower extremity motor nerve dysfunction, dysreflexia, or loss of bowel or bladder function requires prompt evaluation for spinal root impingement or cord compression (cauda equina syndrome).

Pathologic fractures as a result of metastatic bone disease results in acute pain and disability. Vertebral crush fractures will often result in height loss, pain, and can be the initial symptom of bone metastases. Other weight-bearing bones such as long bones and the hip result in the most disability.

Diagnosis

The diagnosis of metastatic bone disease often relies on radiographic methods followed by biopsy of the area in question, especially in a patient without an established diagnosis of malignancy. For patients with high clinical suspicion, plain radiographs are indicated for initial evaluation of focal bone pain. Plain films have a reported sensitivity of 60% and specificity of 99.5% for diagnosing vertebral metastases.³³ Most lesions are described as either lytic or sclerotic; in reality skeletal metastases are typically mixed, and plain radiographs of affected areas are often abnormal. Radionuclide bone scan can confirm the diagnosis as the nuclear tracer, typically technetium-99, has affinity at sites of active bone formation, whether the sites are lytic or sclerotic. Bone scans are more sensitive than plain films for osteoblastic metastases because increases in blood flow and bone mineral turnover that are detected by bone scans are evident earlier than radiographic evidence of overt bone remodeling.³⁴ In case of a diagnosis of a malignancy with a predilection for bone, radionuclide bone scans are the diagnostic test of choice for determining stage of disease. Magnetic resonance imaging (MRI) can also be utilized when results of plain films or bone scans are in question. They are particularly helpful at imaging soft tissues surrounding suspected bone metastases. The sensitivity of MRI for the diagnosis of spine metastases is 83–93% with a specificity of 90–97%.³⁴ The use of diffusion-weighted and contrast enhancement allows accurate differentiation be-

tween benign and malignant processes.^{35,36} In a patient with suspected cauda equina syndrome, MRI provides excellent views of the vertebral column and spinal cord.

While laboratory studies are unable to definitively diagnose skeletal metastases, several are helpful in monitoring progression in established cases. A marked elevation of the alkaline phosphatase in a patient with malignancy would raise the possibility of hepatic or skeletal involvement. An increase in the bone-specific alkaline phosphatase would indicate an increase in bone mineral turnover and the likely presence of skeletal metastases. Peptide byproducts produced during the formation of collagen are helpful in monitoring osteoporosis therapies and may also be beneficial in monitoring progression of skeletal metastases. The major organic component of bone matrix is type I collagen. The complex biosynthesis of collagen by the osteoblast releases soluble propeptide fragments, which can be assayed as a marker of new bone formation and osteoblastic activity. Similarly, osteoclastic bone resorption releases fragments from cross-linked collagen, which can be assayed as markers of bone destruction. These markers can be used to monitor active bone remodeling in patients and the responses to bisphosphonate treatment.³⁷ Bone formation markers include bone-specific alkaline phosphatase and serum procollagen I amino-terminal propeptide (PINP), while resorption markers include urinary collagen cross-linked N-telopeptide (NTX), collagen I carboxy-terminal telopeptide (CTX), pyridinolines (PYD), and deoxypyridinolines (DPYD). Bone formation and resorption markers are often increased in prostate cancer patients with osteoblastic metastases. However, such markers, especially those of resorption, can also be increased as a consequence of bone loss due to androgen deprivation therapy and cannot be used alone to diagnose bone metastases. For example, NTX is not as sensitive as bone scan for the diagnosis of bone metastases, but it may provide an auxiliary diagnostic index for bone scan.³⁸ There is evidence, however, that markers of bone turnover can aid the clinician in determining the response to therapy.³⁹ NTX is the most sensitive in that respect.⁴⁰

Treatment of Bone Metastases

Hormone Therapies

The treatment of metastatic bone disease often requires a multidisciplinary approach involving a medical oncologist, a radiation oncologist, and a surgeon. Systemic chemotherapeutic agents are often used and can have beneficial effects in bone metastases. Endocrine treatments for breast and prostate cancer are considered first-line therapies for hormone-responsive tumors. The use of selective estrogen receptor modulators such as tamoxifen—and possibly raloxifene and toremifene—has been shown to be beneficial in the primary and secondary prevention of breast cancer.⁴¹⁻⁴⁴ Aromatase inhibitors have recently been approved for use in postmenopausal patients with advanced disease, and they show great promise.⁴⁵ Androgen blockade in men with advanced prostate cancer can reduce tumor burden and bone pain. The use of luteinizing hormone-releasing hormone (LHRH) agonists

and antiandrogens are effective and are often preferred over older treatments such as orchiectomy. However, most prostate cancers will overcome androgen blockade in several years and transform to androgen independence.

External Beam Radiation

Prophylactic external beam radiation to prevent fracture in weight-bearing bones in conjunction with surgical fixation can prevent significant morbidity. The use of external beam radiation in the treatment of focal bone pain is also quite effective.⁴⁶ Patients with extensive bone metastases can undergo hemibody irradiation but at the expense of increased toxicity. Controversy exists on the optimum dose and schedule of therapy. Multiple studies have examined whether higher doses of radiation with shorter fractions are more beneficial than lower doses and more fractions, but no study has been convincing. A recent meta-analysis demonstrated no significant difference in pain scores using single or multifraction therapy for palliative treatment.⁴⁷ A survey of American radiation oncologists revealed different practice methods between physicians in the United States and those in Canada. Most radiation oncologists in the United States employ 30 Gy in 10 fractions while 20 Gy in 5 fractions is often used in Canada.⁴⁸

Radioisotopes

Radioisotopes with an affinity for bone have been studied in patients with metastatic breast and prostate cancer with painful bony metastases. Phosphorus-32 was used in the past but had been surpassed by newer agents. Strontium-89 (⁸⁹Sr) is a high-energy beta-particle-emitting radioisotope that has been shown to be effective in decreasing pain. In one study, patients with prostate cancer and metastatic bone disease were randomized to receive either ⁸⁹Sr or external beam radiation (focal or hemibody depending on the extensiveness of the metastases).⁴⁹ Both treatments were highly effective, although there was no significant difference in pain relief scores. However, patients randomized to the ⁸⁹Sr treatment had fewer subsequent painful bony sites, and this result was likely due to the systemic nature of this therapy. The radioisotope samarium-153 (¹⁵³Sm) is also effective in alleviating pain in bone metastases⁵⁰ and has several advantages over ⁸⁹Sr. ¹⁵³Sm has a shorter half-life (2 days) and can therefore deliver larger doses over a shorter time. This radioisotope emits a lower energy particle that can translate into reduced bone marrow toxicity.

Surgery

Prophylactic surgical correction of bone metastases is indicated for impending fractures in weight-bearing bones. Osteolytic lesions that encompass a large area of bone have a high likelihood of fracture, with the highest prevalence of breast and kidney metastases.⁵¹ Fracture from osteoblastic metastases from malignancies such as prostate is unusual. Although pathologic fracture at any location can result in significant pain, fracture of the femur, humerus, pelvis, and vertebrae result in the most disability and fixation at those locations is indicated. Management of impending fracture includes plate osteosynthesis, nailing, and insertion of pros-

thetic implants.⁵² Adjuvant radiotherapy after fixation can inhibit further metastatic destruction.

Spinal cord or cauda equina compression by a spinal metastasis is a medical emergency requiring prompt evaluation and treatment in order to preserve and protect neurologic function. In addition to focal back pain, radicular symptoms and signs include lower extremity muscle weakness, loss of bowel/bladder function, and ataxia. Plain films have limited value in this situation, and evaluation with MRI or myelography to identify the presence of a spinal lesion and cord compromise is required. High-dose corticosteroids in conjunction with external beam radiation or surgical decompression can result in significant return of neurologic function if treatment is initiated within 24–36 hours of symptoms.⁵³ Until recently, laminectomy was the preferred management in patients with cord compression, but recent studies have shown no differences in outcome with radiation therapy.⁵⁴ Therefore, radiation therapy with corticosteroids is considered first-line therapy.

Bisphosphonates

Bisphosphonates are unique in the treatment of metastatic bone disease as this is a bone-targeted therapy. The use of bisphosphonates in the treatment of osteolytic bone disease due to breast cancer appears to have benefit. Two large trials have been published evaluating pamidronate in patients with stage IV breast cancer; the data were later combined in order to evaluate long-term benefit.⁵⁵ Patients were randomized to pamidronate 90 mg or placebo every 3–4 weeks, and the primary outcome was skeletal events per year and time to first skeletal-related event (SRE). Despite a significant number of participants not completing the study, the number of events per year in the treatment group was 2.4, compared with 3.7 in the control group. Also, the median time to the first SRE was longer in the treatment group.

A phase II trial evaluating the effective dose of zoledronic acid compared with pamidronate in patients with osteolytic lesions due to multiple myeloma or metastatic breast cancer was published in 2001.⁵⁶ Zoledronic acid in doses of 0.4 mg, 2.0 mg, or 4.0 mg was compared to 90 mg of pamidronate administered every 4 weeks up to 10 months. The primary endpoint was the need for radiation therapy to bone during the treatment period. Secondary endpoints included SRE, bone mineral density, and bone pain. The 2.0 mg and 4.0 mg zoledronic acid groups had an equivalent rate of radiation therapy requirement as the pamidronate arm, but the 0.4 mg zoledronic acid group underwent radiotherapy at a higher rate. A follow-up phase III trial with a similar patient population compared zoledronic acid 4 mg and 8 mg with pamidronate 90 mg infusion given every 3–4 weeks for 12 months.⁵⁷ SRE was the primary endpoint over 25 months. Due to decline in renal function in patients randomized to 8 mg of zoledronic acid, this dose was reduced to 4 mg. Zoledronic acid reduced the risk of skeletal complications by 16% compared to pamidronate. The oral bisphosphonate clodronate may have benefit in

preventing SRE,^{58,59} but it has not been approved for use in the United States.

The use of bisphosphonates in the treatment of prostate cancer has been controversial, as bone metastases are usually osteoblastic, and bisphosphonates exert their effects via osteoclasts. However, recent studies have shown a benefit. Patients with hormone-refractory metastatic prostate cancer were assigned to receive either zoledronic acid 4 mg, 8 mg followed later with 4 mg, or placebo every 3 weeks for 18 months. Subjects who received zoledronic acid had less SRE and pain compared to the control group, but there was no significant difference in disease progression or performance status.⁶⁰ The use of androgen deprivation therapy in prostate cancer can adversely affect bone mineral density, and the indication for the use of bisphosphonates in this situation is clearer. One study in men with early-stage hormone-responsive disease being treated with androgen ablation therapy showed that 4 mg of zoledronic acid administered every 3 months for 1 year had an increase in lumbar spine bone mineral density compared to a decrease in the control group.⁶¹

Zoledronic acid has been effective in the treatment of bone metastases from other solid tumors, including lung, kidney, and colorectal. In a recent phase III trial, 733 patients with metastatic bone disease were randomized to zoledronic acid 4 mg or placebo. Infusions were administered every 3 weeks for treatment duration of 21 months. The treatment group had a statistically significant reduction in time to first SRE but without affecting mortality.⁶² Of note is the fact that patients in most bisphosphonate trials received supplementation with calcium and vitamin D. This often-neglected detail is important, because the use of bisphosphonates in the presence of vitamin D deficiency may further impair bone mineralization.

A major morbidity for patients with skeletal metastases is intractable bone pain, which is reduced by bisphosphonate treatment.⁶³ The mechanisms of pain caused by bone metastases are specific and complex. Factors produced by tumor cells, as well as molecules released by bone remodeling, stimulate pain receptors in bone.⁶⁴ Interruption of the vicious cycle with bisphosphonates can thus reduce the concentration of pain-stimulating molecules in the microenvironment surrounding metastatic tumor cells.

Substantial controversy surrounds clinical data on the effects of bisphosphonates on breast cancer tumor burden at extraskelatal sites.^{65,66} As discussed above, bisphosphonates have direct antitumor actions *in vitro*, but it is unclear whether the compounds reach sufficiently high local concentrations in nonbone sites to have such actions in patients. The bisphosphonates have the potential to enhance antitumor activities of known cytotoxic agents, but further and larger clinical trials are required to address the importance of the preclinical data. *In vitro*, bisphosphonates have direct effects on tumor cells to reduce tumor growth⁶⁷ and invasiveness,^{68,69} as well as to induce apoptosis.^{70,71} Bisphosphonates may also affect other components of the metastatic cascade by reduced adhesion of tumor cells to bone^{72,73} and by inhib-

iting angiogenesis.⁷⁴ In the latter study, zoledronic acid reduced testosterone-induced revascularization of the prostate in rats, the effect of which was due to transient accumulation of the bisphosphonate in the prostate.⁷⁴

Questions still remain regarding the use of bisphosphonates for metastatic bone disease: which is the best bisphosphonate, what is the ideal dose and duration, how should it be administered, should it be given to patients early in the course of the disease, and—most important—do these drugs improve survival? Also, what are the effects of bisphosphonates on the tumor cells themselves? What is the role of bisphosphonate therapy in the treatment of osteoporosis due to cancer treatment, independent of the presence of bone metastases?

ETA Receptor Antagonists

Recent experiments show an important role for tumor-secreted ET-1 in osteoblastic metastases. ET-1 is a potent stimulator of osteoblast proliferation and new bone formation. Tumors secreting ET-1 cause osteoblastic metastasis in an animal model and the metastases can be blocked with an ETA receptor antagonist.²⁶ This antagonist, atrasentan, has completed a phase II clinical trial in men with hormone-refractory prostate cancer.⁷⁵ The agent delayed time to progression and decreased markers of tumor burden. Of particular interest, atrasentan decreased markers of bone remodeling, which were elevated in patients with prostate cancer.²⁷ This result supports the importance of the vicious cycle model, in which targeting one step serves to suppress all parts of the cycle.

Novel Therapies

Although the current therapy for bone metastases results in a significant reduction in morbidity, such therapy does not cause regression of established disease. New therapy is under development to this end. Novel therapies for osteolytic bone disease based on inhibition of the RANK/RANKL system have been proposed, and several are in clinical trial. A phase I trial studying recombinant osteoprotegerin (AMGN-0007) in patients with multiple myeloma or bone metastases from breast cancer was recently published.⁷⁶ However, concerns remain about adverse effects and theoretical concerns of decreasing cancer cell apoptosis. OPG is also a receptor for the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), and this molecule has been shown to be involved in apoptotic signaling in cancer cells. A humanized RANKL antibody, AMG-162, has been developed and has shown promise in phase I clinical trials. The biologic half-life after a single subcutaneous injection was at least 2 months and adverse effects were minimal. In breast cancer patients with metastases to bone, AMG-162 reduced urinary markers of bone resorption.⁷⁷ Integrins also appear to be important in the development of bone metastases.⁷⁸ Mice injected with melanoma cells that result in osteolytic metastases had increased survival when treated with a monoclonal antibody to integrin $\alpha_v\beta_3$.⁷⁹ Integrin inhibitors are currently in phase II human trials.⁸⁰ Vitamin D analogues have shown promise in preclinical models of breast cancer metastasis to bone,

the mechanism of which is unclear but may involve inhibition of tumor growth or of PTHrP production. Humanized PTHrP antibodies are in clinical trials for women with breast cancer metastases to bone, but data regarding efficacy are not yet available. Based on the exponential growth of the mechanisms underlying tumor metastases to bone, we expect many new therapies to be developed in the next 5 years. Possible targets include CTGF, CXCR4, MMPs, TGF β , IL-11, IL-8, and signal transduction inhibitors of the MAP kinase pathway. These new therapies may be useful in combination with the existing bisphosphonate treatments. Future preclinical and clinical trials will determine the importance of these newly identified targets in achieving the ultimate goal to cause regression of established bone metastases and to prevent the development of new disease.

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