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New Opportunities for the Management of Cancer-Related Bone Complications

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Activity Overview

Bone metastasis is a common feature of advanced-stage cancer. Despite a decline in cancer-related death in general over the past decade, the development of bone metastasis is still associated with a marked reduction in 5-year survival rates and significant disease-related morbidity. Patients with bone metastases often experience a reduced quality of life from severe pain and an increased incidence of skeletal-related events, including pathologic fractures, spinal cord compression, and hypercalcemia. Recent advances in understanding of the complex interaction of cancer cells with their microenvironment, as well as of the pathophysiologic mechanisms in bone metastases, are stimulating the development of novel therapeutic options for these patients. Current treatments are aimed at lessening the impact of existing bone metastases. Novel therapies directed toward modulating cancer cell signaling mechanisms and the tumor microenvironment itself are being developed. Such therapies may impede the development of tumor-related metastatic disease as well as provide additional therapeutic options for managing bone loss that results from some of the oncologic therapies commonly employed. This journal supplement presents the latest clinical advances in the management of cancer-related bone complications, especially as related to current knowledge of the pathophysiology involved. A discussion of new and emerging therapies is also featured.

Target Audience

This activity has been designed to meet the educational needs of medical oncologists, urologic oncologists, urologists, radiation oncologists, hematologist-oncologists, and other health care providers who manage patients with cancer that has metastasized or has the propensity to metastasize to bone.

Learning Objectives

Upon completion of this activity, participants should be able to:

- Recognize the clinical impact of bone metastases with respect to skeletal-related events
- Summarize the pathophysiology of bone metastasis
- Describe the current standard for the treatment and prevention of skeletal-related events in patients with cancer that has metastasized to the bone
- Assess the risks and benefits associated with current therapies for bone metastasis
- Evaluate the clinical data on the appropriate use of novel agents in development for the prevention and treatment of bone metastases as well as the prevention and treatment of bone loss secondary to oncologic therapies
- Compare and contrast the mechanisms of action of bisphosphonates and novel bone-targeting agents

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Medium

A journal supplement was selected as the instructional format to accommodate the learning preferences of a significant portion of the target audience.

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Toremifene	Fareston®	Treatment of metastatic breast cancer in postmenopausal women with estrogen receptor–positive tumors	Treatment and prevention of cancer therapy–induced bone loss in prostate cancer patients receiving GnRH agonist therapy
Zoledronic acid	Zometa®	Treatment of hypercalcemia of malignancy; multiple myeloma; solid tumors with documented metastasis to bone (in conjunction with standard antineoplastic therapy); prostate cancer that has progressed after hormonal therapy	Prevention of bone metastases; direct antineoplastic effect when used in combination with standard antineoplastic therapies; treatment and prevention of cancer therapy–induced bone loss

New Opportunities for the Management of Cancer-Related Bone Complications

Introduction

Patients with cancer are at risk for many events involving the skeleton, including metastatic disease of bone and treatment-related bone loss. Advanced cancers, particularly breast, prostate, and lung cancer, frequently metastasize to the bone, and bone involvement is also characteristic of multiple myeloma.[1] In early-stage cancer, patients are at risk of accelerated bone loss and skeletal complications as a result of anticancer treatments that deplete gonadal hormones and adversely affect bone health.[2] The skeletal complications resulting from bone loss cause serious morbidity, undermine the quality of life, and increase mortality. Preservation of skeletal health is therefore an important aspect of patient care in the oncology setting.

The past decade has witnessed a tremendous increase in our understanding of the biology and treatment of metastatic bone disease. The balance of osteoblastic bone formation and osteoclastic bone resorption that characterizes normal bone metabolism is disturbed when tumor cells enter the bone environment. Patients who have cancer show variable patterns of bone effects, ranging from mostly destructive, or osteolytic, in breast cancer and multiple myeloma to primarily osteoblastic in prostate cancer. As molecular mechanisms responsible for osteolytic and osteoblastic metastasis have been identified, new molecular targets for treating bone metastases have emerged.[3,4]

Bisphosphonates reduce bone resorption and increase bone density and are currently used to prevent skeletal complications from metastatic bone disease.[5,6] The role of these agents in the treatment of cancer patients continues to expand. The problem of bone loss caused by cancer treatment is becoming an increasing concern as more patients are being treated with effective hormonal anticancer therapies that nonetheless produce adverse skeletal effects. Strategies involving bisphosphonates similar to those used to treat noncancer-related osteoporosis are proving effective in mitigating the risk of bone loss from cancer treatment.[7] Because preclinical studies with bisphosphonates have suggested a direct effect on tumor progression, these agents are also being studied earlier in the course of treatment for several different types of cancers. Large trials in breast and prostate cancer are assessing an expanded role for these agents as adjuvant therapy for prevention of bone metastases.[8] In addition to exploring new directions with bisphosphonates, attention is also being focused on ways to optimize therapy with these agents through appropriate patient selection and mitigation of adverse effects. Along with the bisphosphonates, a number of new drugs targeting the pathogenetic pathways of bone destruction are under clinical investigation as additional treatment options for bone complications.[9]

This supplement examines the scope of metastatic and cancer treatment–induced bone disease with a focus on breast cancer, prostate cancer, and multiple myeloma, which are among the cancers in which bone involvement most frequently occurs. Current concepts underlying the pathophysiology of bone destruction in these diseases are reviewed as a foundation for understanding the rationale for the use of current bone-directed therapies and the development of new agents. Discussion of the management of cancer-related bone involvement will focus on the clinical efficacy and safety of currently available treatments as well as of emerging therapies.

Impact of Bone Metastasis

Metastasis is the single most catastrophic complication of cancer. Disease that has spread to other sites is more often the cause of death than is the primary tumor. The skeleton is the preferred site of metastasis for many solid tumors, particularly breast and prostate cancer (Table 1).[1] The high prevalence of skeletal disease in breast and prostate cancer reflects both the high incidence of these malignancies and the relatively long clinical course of these diseases after diagnosis of bone metastasis. Approximately 65–75% of patients dying of breast or prostate cancer have metastatic bone disease on postmortem examination, compared with 30–40% of patients with lung, thyroid, or kidney cancer.[10] Almost 100% of patients with advanced multiple myeloma have bone involvement.

Risk of Skeletal Involvement

Breast Cancer

Breast cancer is the most prevalent solid organ tumor in women and was diagnosed in more than 182,000 women in 2008.[11] More than 40,000 women succumbed to breast cancer in 2008.[11] Despite advances in the management of early breast cancer, many women will develop metastatic bone disease. The median survival of breast cancer patients after a diagnosis of bone disease is approximately 20 months.[1] Patients whose disease is confined to the skeleton have longer survival than do patients whose disease subsequently develops at extraskeletal sites.[10] However, rates of skeletal complications are higher among women with bone-only metastases at first relapse (81%), compared with rates for women with both bone and extraosseus metastases (60%) or without bone metastases (21%).[10]

Evaluation of the placebo arms of randomized controlled studies of bisphosphonates has provided insight into the natural history of malignant bone lesions in breast cancer and their complications. In clinical trials, a skeletal-related event (SRE) occurred within 1 year in more than 50% of patients with metastatic breast cancer who did not receive bisphosphonate therapy;[12,13] the median time to the first SRE ranged between 5 and 16 months.[14] A study using serial radiographic examinations in patients with breast cancer indicated that a woman with bone metastases from breast cancer will experience, on average, 1.3 vertebral and 0.4 nonvertebral fractures per year.[1]

Table 1. Incidence of Bone Metastases and Related Prognosis in Various Types of Cancer[1]*

	Incidence of advanced disease (%)	Median survival (months)	5-Year survival (%)
Myeloma	95–100	20	10
Breast	65–75	24	20
Prostate	65–75	40	25
Lung	30–40	<6	<5
Kidney	20–25	6	10
Thyroid	60	48	40
Melanoma	14–45	<6	<5

Data from Cancer, vol. 80, no. 8 suppl, 1997, pgs. 1588-1594, 1997, © American Cancer Society Reproduced with permission of John Wiley & Sons, Inc.

*Improved survival has been reported for several malignancies more recently.

Prostate Cancer

Prostate cancer is the most prevalent solid organ tumor in men. An estimated 186,000 new cases of prostate cancer occurred in 2008, with more than 28,000 deaths.[11] At presentation, approximately 10% of men have bone metastases, and almost all patients who die have skeletal involvement.[10] The clinical course of patients with metastatic prostate cancer can be relatively long: the median survival for patients with cancer that is confined to the bone is 53 months, compared with 30 months for patients with additional visceral disease and only 12 months for those with both bone and visceral metastases and poor performance status.[1]

The degree of skeletal morbidity in patients with metastatic prostate cancer not receiving bisphosphonate therapy can be illustrated by the outcome of patients in the placebo arm of a trial evaluating the bisphosphonate zoledronic acid. Among patients receiving standard cancer treatments alone during the 15-month duration of the trial, 44% experienced an SRE, 22% had a pathologic fracture, and almost one-third required palliative radiation

Table 2. Incidence of Skeletal-Related Events in Metastatic Bone Disease[14]

Primary disease (Length of follow-up)	Incidence of SREs (%)			
	Breast (24 months)	Myeloma (21 months)	Prostate (24 months)	Lung/Other (21 months)
Total SREs	68	51	49	48
Radiation to bone	43	34	33	34
Pathologic fractures	52	37	25	22
Hypercalcemia of malignancy	13	9	1	4
Surgery to bone	11	4	4	5
Spinal cord compression	3	2	8	4

therapy for bone pain.[15] An extension of this study revealed the increased risk of additional SREs incurred by patients with a history of SREs.[16]

Multiple Myeloma

Multiple myeloma is the second most common hematologic malignancy in the United States,[17] accounting for an estimated 20,000 new cases in 2008.[11] Bone destruction and skeletal complications are characteristic of the disease and are observed on radiographs in 79% of patients at diagnosis.[18] The median survival for patients with multiple myeloma is 2–3 years, and 5-year survival is 15–25%.[1] Without bone-directed therapy, the risk for skeletal events increases progressively over time. In a large randomized trial involving patients with multiple myeloma who received chemotherapy, the rates of skeletal events at 12, 48, and 84 weeks without bisphosphonate therapy were 21%, 48%, and 58%, respectively; rates of pathologic fracture at these time points were 9%, 37%, and 46%, respectively.[19,20] On average, patients with multiple myeloma experienced 2 skeletal events per year.[20]

These findings indicate that although the diagnosis of malignant bone disease generally signifies that the cancer is incurable, patients with bone metastases may survive for extended periods and continue to be at risk for developing skeletal complications.

Skeletal Complications

Clinical Features

Skeletal malignancies cause considerable morbidity, including pain, impaired mobility, pathologic fracture, spinal cord or nerve root compression, hypercalcemia of malignancy, and need for surgery or radiotherapy for bone metastasis–related complications. The frequency of SREs across different types of tumors in patients not receiving bisphosphonates is shown in Table 2.[14] Skeletal morbidity rates in the placebo arms of bisphosphonate trials indicate that, on average, a patient with metastatic disease will experience an SRE every 3 to 6 months.[10] The most frequent complications are pathologic fractures and bone pain requiring radiation therapy.

Cancer-associated pain results mainly from bone metastases and often requires palliative radiotherapy. Bone pain is a significant problem in both community and hospital practice. Structural damage, periosteal irritation, and nerve entrapment are common causes of bone pain. Bone resorption also appears to be a major cause of bone pain, and symptomatic improvement after bisphosphonate therapy appears to be linked to inhibition of bone resorption.[1]

Pathologic fractures and spinal cord compression are some of the most debilitating consequences of bone destruction in metastatic disease. Vertebral fractures can cause vertebral deformity or collapse, resulting in significant back pain, postural changes, and functional impairment. Spinal cord compression can lead to severe neurologic sequelae, including paraplegia, if the compression is not relieved within 24 to 48 hours.[1] Long-bone fractures due to cancer often never heal or heal with difficulty and require surgical intervention and lengthy physical rehabilitation to restore function.[21]

Hypercalcemia is the most common metabolic complication of breast cancer and is a major concern in any malignancy causing osteolytic lesions. Lysis of bone leads to elevated levels of serum calcium and associated symptoms such as fatigue, nausea, vomiting, dehydration, and mental status changes. The mechanism of hypercalcemia involves production of parathyroid hormone–related protein and other bone-resorbing cytokines by tumor cells. Patients with cancer-related hypercalcemia almost invariably have advanced disease.[22]

Morbidity and Costs

SREs are associated with greater mortality. In patients with prostate cancer, skeletal fracture is an independent and adverse predictor of survival, regardless of the pathologic stage of disease. Among 195 men with or without a history of skeletal fracture after a diagnosis of prostate cancer, median overall survival was 121 and 160 months, respectively (P=.04).[23] A retrospective analysis, using data from 3 bisphosphonate trials to examine the relationship between pathologic fractures and survival in patients with metastatic bone disease or multiple myeloma, found that, in all types of tumors other than lung, pathologic fractures were associated with a significantly increased mortality risk. This increased mortality risk in patients with fractures, relative to the risk in those without a fracture, was highest for breast cancer (32%) but somewhat lower for prostate cancer or multiple myeloma (an approximately 20% higher risk).[24] The association between pathologic fractures and death was present regardless of bisphosphonate treatment.[24]

Skeletal complications can have a debilitating effect on the quality of life of cancer patients, substantially reducing their well-being and functional independence. A study that evaluated the impact of bisphosphonate treatment on measures of health-related quality of life in men with advanced prostate cancer and bone metastases showed that significant declines in physical, functional, and emotional well-being were present in patients with SREs, particularly after radiation to bone.[25]

Bone complications are also associated with increased health care costs. A retrospective study in patients with metastatic prostate cancer showed that, for each patient, $9,783 of health care costs were directly attributable to skeletal complications.[26] Furthermore, patients with SREs incurred $20,484 more in total medical costs than did patients without SREs. Another study, in patients with metastatic lung cancer, reported the expected costs of care directly attributable to SREs at $9,494 per patient; expected total medical costs were $28,223 greater in patients with SREs than in those without SREs.[27] The high marginal cost of skeletal complications suggests that therapies to prevent complications may provide significant health care cost savings.

Without treatment of metastatic bone disease, skeletal morbidity remains a major clinical problem, associated with high rates of fracture and other clinical complications. Once a fracture occurs, the patient is at increased risk of clinical complications that may hasten death. Bone-directed therapies may alleviate many of these skeletal complications, allowing patients to preserve mobility and functional independence and reduce the risk of death.

Bone Pathophysiology in Metastatic Disease

Normal Bone Remodeling

As an organ system, bone undergoes continuous change in response to mechanical stress. The adult skeletal system is characterized by a balanced remodeling sequence consisting of resorption of bone by osteoclasts followed by new bone formation by osteoblasts at the same site. These processes are mediated by growth factors and cytokines released from the bone matrix, as well as from hematopoietic stem cells, immune cells, and stromal cells present in the bone marrow.

Osteoclasts

Osteoclasts arise from progenitor cells in the macrophage-monocyte lineage, which differentiate into inactive osteoclasts. Systemic hormones such as parathyroid hormone, 1,25 dihydroxyvitamin D3, and thyroxine, along with locally acting factors, are important regulators of osteoclast formation and activation. Systemic hormones stimulate osteoclast formation by inducing the expression of receptor activator of nuclear factor κB ligand (RANKL) on marrow stromal cells and osteoblasts. RANKL is a potent inducer of osteoclast formation, and its binding to RANK receptors on osteoclast precursors triggers intracellular events that lead to their activation. This process is kept in check by osteoprotegerin, a decoy receptor for RANKL, which inhibits the differentiation and resorption activities of osteoclasts. The RANKL/RANK/osteoprotegerin triad is thus a key regulator of bone resorption. The bone milieu also contains other locally produced osteoclast-stimulating cytokines such as interleukin-6 (IL-6), IL-1, IL-17, and colony-stimulating factors, as well as inhibitory agents such as IL-4, IL-18, and interferon γ.[28]

Osteoclasts must adhere to bone for resorption to occur. On contact with bone or other mineralized tissue, multinucleated osteoclasts develop a polarized phenotype that is unique to their resorptive function. The ruffled border of the plasma membrane of osteoclasts faces bone and is the resorbing organelle of the cell. Proteases and hydrogen ions secreted by osteoclasts are released across the ruffled border to dissolve the bone matrix and create an acid microenvironment that leads to demineralization of bone under the plasma membrane. The physical intimacy between the ruffled border and juxtaposed bone is mediated by integrins. These are receptors expressed by differentiating osteoclast precursors that recognize a specific amino acid motif in bone matrix proteins.[28,29] At the end of the bone-resorbing cycle, the osteoclast undergoes apoptosis. Agents that enhance apoptosis, such as bisphosphonates, or that interfere with osteoclast adherence or protease activity, may potentially be useful for treating bone metastases.

Osteoblasts

The differentiation of osteoblasts is not as well characterized as that of osteoclasts. Osteoblasts are bone-forming cells that arise from mesenchymal stem cells, which also form adipocytes and muscle cells. Alkaline phosphatase is produced during early development, whereas osteocalcin and calcified matrix are synthesized as the cells mature. Osteoblasts eventually mature into osteocytes.[28]

The proliferation and differentiation of osteoblasts is regulated by systemic hormones and growth factors such as bone morphogenetic proteins, transforming growth factor-β (TGF-β), insulin-like growth factor, and fibroblast growth factor, which are released from bone matrix following osteoclastic activity. High levels of TGF-β may signal apoptosis in osteoclasts and thus halt further bone resorption.[3,28]

Metastatic Bone Disease

The normal balance of bone resorption and formation is disturbed by cancer. The metastasis of tumor cells to bone requires a complex series of events involving detachment of tumor cells from the primary tumor site, invasion of the vasculature, migration and adherence to capillaries of the bone, extravasation, and invasion and proliferation in bone marrow. Invasion of tumor cells disturbs the coordinated relationship between osteoclastic and osteoblastic functions and creates a dysregulated environment in which cytokines and growth factors promote tumor cell proliferation and bone destruction.

The patterns of bone effects in patients with cancer differ, ranging from mostly destructive, or osteolytic, as seen in breast cancer and multiple myeloma, to mostly bone forming, or osteoblastic, as seen in prostate cancer. These represent two extremes, and in most patients, bone metastases involve both elements to varying degrees. The predominance of either an osteolytic or osteoblastic

appearance in the final lesion is influenced by the balance of factors generated by the interaction of a particular tumor with the bone environment. The "seed and soil" concept, articulated more than a century ago, remains central to understanding the pathophysiology of cancer metastasis, as well as serving as a guiding principle in the development of therapies targeted at disrupting tumor-bone interactions within the microenvironment of bone.

Osteolytic Lesions

Osteolytic lesions are caused by the activity of osteoclasts, not by the direct effects of cancer cells on bone. The factors responsible for activating osteoclasts may vary depending on the tumor.

Multiple Myeloma

In multiple myeloma, bone osteoclasts aggregate only at surfaces adjacent to myeloma cells, and bone resorption occurs only in tumor-involved areas. In addition, bone formation is suppressed; thus, the bone lesions in multiple myeloma are purely lytic.[28]

Several cytokines have been implicated in the increased osteoclastogenic activity in multiple myeloma, including IL-6, RANKL, and macrophage inflammatory protein-1α (MIP-1α). IL-6 appears to be an important mediator of tumor growth and bone resorption, as suggested by its presence in marrow plasma samples from patients with myeloma, an association between increased serum concentrations of soluble IL-6 receptor and poor prognosis, and stimulation of production of stromal IL-6 after adherence of myeloma cells.[21,28] RANKL is a major regulator of myeloma disease in bone, as evidenced by an increase in its production by stromal cells in the bone microenvironment in myeloma, reduced expression of osteoprotegerin, and suppression of bone disease by RANKL blockade.[28] MIP-1α, which is secreted from most myeloma cells, is another potent inducer of osteoclast formation and a key regulator of bone destruction. MIP-1α enhances RANKL-stimulated and IL-6–stimulated osteoclast activation. Its level is increased in bone marrow plasma, and increased levels correlate with the presence of osteolytic lesions. By upregulating integrin expression on myeloma cells, MIP-1α also facilitates adhesive interactions between tumor and stromal cells that induce RANKL expression by stromal cells, leading to osteoclast differentiation and activation.[28] These observations suggest that interactions of myeloma cells and osteoclasts contribute to an escalating pattern of bone destruction and tumor growth.

Osteoblastic activity is profoundly impaired in multiple myeloma, but the mechanism of impaired bone formation remains poorly understood. Preliminary findings suggest that disturbances in the Wnt signaling pathway are implicated in the suppressed osteoblastic response in myeloma.[30,31] Production of dickkopf-1 (DKK1) and soluble frizzled related protein 2, and expression of the transcription factor RUNX2, both positively regulate osteoblast differentiation and bone formation.[32,33]

Breast Cancer

Breast cancer is associated predominantly with osteoclastic activity. The primary activator of osteoclastogenesis is parathyroid hormone–related peptide, which is overproduced by breast cancer cells. This hormone induces RANKL expression on stromal cells and inhibits osteoprotegerin secretion from stromal cells and osteoblasts, thereby stimulating the differentiation of osteoclast precursors into bone-resorbing osteoclasts. Active growth factors such as TGF-β, insulin-like growth factor, and fibroblast growth factor, released from demineralized bone matrix, stimulate the proliferation of tumor cells and further production of parathyroid hormone–related peptide, resulting in a "vicious cycle" of escalating bone loss and tumor growth. Breast cancer cells also secrete other mediators such as IL-6, IL-1, tumor necrosis factor α, and prostaglandin E2, which also stimulate osteoclast formation.[28]

The close relationship between tumor growth and bone destruction in multiple myeloma and breast cancer has important therapeutic implications since it suggests that inhibitors of osteolysis may also decrease tumor burden. The first and best studied approach to the treatment of bone loss associated with breast cancer is the use of bisphosphonates to directly slow osteoclastic degradation of bone (see below). Newer approaches are being investigated that exploit recent understanding of metastatic bone disease.

Osteoblastic Lesions

Prostate Cancer

The characteristic bone metastatic lesion associated with prostate cancer cells is osteoblastic. New woven bone is deposited by osteoblasts in a disorganized manner, interlaced between foci of tumor cells. Even though osteoblastic lesions are associated with increases in both osteolysis and bone formation, the sites of bone resorption and bone deposition are uncoupled. This results in excessive new bone being deposited away from the site of resorption. The result is lower bone strength and increased risk of fractures and vertebral collapse.

Prostate cancer cells express several factors that may stimulate osteoblast differentiation and proliferation. Among these are bone morphogenetic proteins, TGF-β, fibroblast growth factor, Wnt inhibitors, and

endothelin-1.[3,4] Tumor-produced endothelin-1 stimulates bone formation and osteoblast proliferation by decreasing synthesis of the Wnt pathway inhibitor dickkopf and is considered to be a major inducer of the osteoblastic response to metastases.[34] An antagonist to the endothelin receptor that reduces the tumor-induced osteoblastic response is being evaluated in clinical trials.

The osteolytic component of prostate cancer bone metastasis has been appreciated only recently. Histomorphometric studies have documented eroded surfaces and an elevation of osteolysis markers in patients with bone involvement.[4] In the bone environment, prostate cancer cells express factors such as parathyroid hormone–related peptide, IL-1, IL-6, and RANKL, which promote osteoclastogenesis. In turn, the degradation of bone associated with these lytic events releases a number of growth factors (for example, TGF-β) stored in the bone matrix that promote prostate cancer cell growth and perpetuate an escalating cycle of growth and destruction, as in breast cancer. Therapeutic approaches similar to those in breast cancer and multiple myeloma are therefore also used to target the osteolytic response in prostate cancer metastases.

Management of Bone Metastases

Diagnosis

Pain in the spine is often the first symptom of metastasis to bone. Progressive pain in older individuals, pain in patients with a history of cancer, weight loss, and pain that worsens at rest should alert the physician to the possibility of metastatic bone disease. In some instances, a fracture may be the first sign of bone disease. Problems with urination may signal spinal compression that puts pressure on the nerves supplying the bladder.[34] Cancer metastasis to bone can result in hypercalcemia, which may cause nausea, loss of appetite, constipation, and tiredness; in extreme cases, it may lead to renal failure, cardiac arrhythmias, and death.[10]

Imaging tests have traditionally been used to evaluate the extent and severity of metastatic bone disease and to identify the characteristics of complications. Imaging tests have also been used to assess response to treatment.[35] Plain radiographs can detect bone lesions and identify bones at risk of fracture. This method has low sensitivity, however, demonstrating lytic disease only when at least 30% of bone substance has been lost.[35] Radionuclide bone scans using a technetium 99-phosphorus compound are less sensitive than radiography at showing foci of osteolytic disease, although they may be helpful in evaluating areas not well revealed by radiographs. Overall, scintigraphy is less useful in assessing osteolytic malignancies because the radionuclide is incorporated into bone areas of increased mineralization. The presence of lytic lesions such as those that occur in multiple myeloma or breast cancer may thus be missed with this method.[35] Although bone scans can underestimate the extent of purely osteolytic lesions, they are very useful in detecting osteoblastic lesions. The National Comprehensive Cancer Network (NCCN) recommends bone scans for several categories of prostate cancer patients: symptomatic patients as well as nonsymptomatic patients with a life expectancy of more than 5 years; patients with T1 to T2 disease in the presence of a prostate-specific antigen (PSA) level greater than 20 ng/mL; patients with a Gleason score of 8 or higher; or those with T3 to T4 disease.[36] Bone scans are also recommended in post–radical prostatectomy patients, specifically, in those who develop an undetectable PSA level that becomes greater than 0.3 ng/mL and rises on two or more determinations or in those who develop a rising PSA following radiotherapy.

Computed tomography scanning is more sensitive than radiography at detecting small lytic lesions and is recommended when radiographic findings are ambiguous and when symptomatic areas do not show abnormalities on plain films.[37] This technique, along with magnetic resonance imaging (MRI), is useful for assessing the extent and nature of any associated soft-tissue disease. MRI is preferred for investigating patients with spinal cord compression. Because MRI allows visualization of large volumes of bone marrow without radiation exposure, this technique is also favored for visualizing disease within the bone marrow.[35]

Positron emission tomography and technetium-99 sestamibi scanning are newer imaging techniques under evaluation. Positron emission tomography, which uses injected radioactive glucose, is useful for detecting the spread of cancer. In technetium-99 sestamibi imaging, a radioactive tumor-seeking tracer is injected to identify areas of active disease. This technique has shown high specificity and sensitivity in the detection of bone lesions in multiple myeloma. However, it may be less sensitive than MRI in identifying spinal lesions. These methods are not generally recommended for routine use but may be appropriate in selected cases requiring clarification of previous imaging findings.[35]

Currently, no laboratory test can diagnose skeletal metastases definitively. Serum tumor markers are often followed to evaluate disease progression or response to therapy. A high blood calcium level may signify spread to bone and destruction of bone. Very high PSA levels in men with prostate cancer who have undergone surgery or radiation therapy may signify the spread of cancer to the bone. Markers of bone metabolism include N-telopeptide of type 1 collagen (NTx), a highly specific marker of osteolysis, and bone-specific alkaline phosphatase, a marker of bone turnover. Preliminary evidence suggests that levels of NTx may have prognostic value for predicting skeletal complications.[38]

Treatment

The main goal of treatment for bone metastases is to prevent skeletal complications and the resulting morbidity, loss of independent functioning, and reduced quality of life. The treatment of bone metastases requires a multidisciplinary approach that incorporates systemic

therapies aimed at the tumor as well as therapies that interrupt the process of bone breakdown. Bisphosphonates are increasingly the treatment of choice for attenuating the skeletal complications of cancer, but other treatment options include traditional therapies such as radiotherapy, radiopharmaceuticals, surgery, vertebroplasty, and kyphoplasty.[39]

Traditional Therapies

External-beam radiotherapy often provides excellent relief of metastatic bone pain. Relatively low doses of radiation are required, and the treatment may be repeated if symptoms recur. A single 8-Gy dose is widely accepted to provide effective pain control.[37] Radiation may also be used to prevent or treat fractures and to prevent spinal cord compression.[39] Radiopharmaceuticals are an effective alternative to radiotherapy for the palliation of bone pain. Intravenously administered isotopes such as strontium-89 or rhenium-186 are short-term emitting radionuclides that can treat multiple lesions simultaneously. These agents are preferentially taken up by osteoblastic bone and, in addition to producing an analgesic effect, also have a local antitumor effect. Because of the potential for bone marrow suppression, radioisotope treatment is recommended mainly for patients with multiple painful sites and good bone marrow function.[40]

Surgery can effectively relieve neurologic symptoms and provide pain relief in patients with vertebral collapse, but it is associated with a major complications rate of 5–13%. Currently, the preferred approach to spinal metastases is to follow surgical treatment with radiotherapy.[40] Vertebroplasty or kyphoplasty are alternatives to surgery that may be indicated for patients who have refractory spinal pain without neurologic compromise. These procedures involve percutaneous injection of a cement into the collapsed vertebrae, which results in stabilization of fractures. Compared with radiotherapy, these procedures provide immediate spinal stability.[40]

Bisphosphonates

Bisphosphonates inhibit osteoclast-mediated bone resorption and are currently the mainstay for long-term treatment of osteolytic bone disease. They bind preferentially at bone surfaces undergoing active metabolism and are released from the matrix during bone resorption. Newer nitrogen-containing bisphosphonates such as zoledronic acid, pamidronate, and ibandronate inhibit the farnesyl diphosphate synthase enzyme in the mevalonate pathway and increase apoptosis of osteoclasts. These agents are orders of magnitude more potent than first-generation non–nitrogen-containing bisphosphonates such as clodronate and etidronate, which induce apoptosis through inhibition of adenosine triphosphate–dependent intracellular processes.[41] Agents currently approved for the treatment of patients with bone metastases are shown in Table 3.[14] Clodronate, an orally administered bisphosphonate, and ibandronate, an intravenously administered agent, are currently marketed only outside the United States for this indication.[14] Intravenous pamidronate was approved by the Food and Drug Administration (FDA) in 1995 to treat bone metastases in patients with multiple myeloma or metastatic breast cancer. Intravenous zoledronic acid was approved in 2002 to treat patients with bone metastases from multiple myeloma or any solid tumor, including breast and prostate cancer.[18]

Table 3. Bisphosphonates Approved for the Treatment of Metastatic Bone Disease[14]

	Relative potency	Dose and administration	Schedule
Non-nitrogen			
Clodronate*	1	1,600 mg orally	Daily
Single nitrogen			
Pamidronate	20	90 mg IV over 2 hr	Every 3–4 wk
Ibandronate*	857	6 mg IV over 1 hr 50 mg orally	Every 3–4 wk Daily
Two nitrogens			
Zoledronic acid	16,700	4 mg IV over 15 min	Every 3-4 wk

*Not approved in the United States.

IV=intravenous.

Most of the trials of bisphosphonates have been performed in patients with metastatic breast cancer or multiple myeloma. A number of clinical endpoints have been used to measure the therapeutic benefits of bisphosphonate therapy. The SRE rate is a composite endpoint that captures the number of patients experiencing a clinically relevant event, defined as pathologic fracture, spinal cord compression, radiotherapy to bone, or surgery. The skeletal morbidity rate is the annual incidence of SREs that takes into account all events occurring during the follow-up period. Other endpoints include time to first SRE and multiple-event analysis, which is a robust method that accounts for the number and timing of all SREs.[42]

Table 4. Bisphosphonate Treatment of Bone Metastases in Breast and Prostate Cancer[12,13,15,43-49]

Treatment	No. of patients	Results	Reference
Breast Cancer			
Pamidronate (90 mg IV) Placebo	382	Reduced proportion experiencing SRE, 43% vs 56% (*P*<.001) Delay in first SRE, 13.1 vs 7.0 months (*P*=.0005)	Hortobagyi et al[13]
Pamidronate (90 mg IV) Placebo	374	Reduced proportion experiencing SRE, 56% vs 67% (*P*=.027) Delay in first SRE, 10.4 vs 6.9 months (*P*=.049)	Theriault et al[44]
Zoledronic acid (4 mg IV) Placebo	228	Reduced proportion experiencing SRE, 30% vs 50% (*P*=.003) Delay in first SRE, Not reached vs 12 months (*P*=.007)	Kohno et al[12]
Zoledronic acid (4 mg IV) Zoledronic acid (4 mg IV) Pamidronate (90 mg IV)	1,130	43% had an SRE with zoledronic acid 4 mg, compared with 45% with pamidronate; 20% risk reduction for an SRE (*P*=.025)	Rosen et al[45] Coleman et al[46]
Prostate Cancer			
Clodronate (2080 mg/day PO) Placebo	311	Improved bone progression-free survival by 21% (*P*=.066) Improved overall survival by 20% (*P*=.082)	Dearnaley et al[47]
Mitoxantrone and prednisone ± clodronate (1500 mg IV every 3 weeks) Placebo	204	Palliative response in 46% in the clodronate arm, 39% in the placebo arm (*P*=.54)	Ernst et al[48]
Pamidronate (90 mg IV every 3 weeks) Placebo	236	No significant benefits in pain or proportion of patients with SREs	Lipton et al[49]
Zoledronic acid (4 mg IV every 3 weeks) Placebo	643	Reduced proportion experiencing SRE, 33% vs 44% (*P*=.021) Delay in first SRE, Not reached vs 321 days (*P*=.01)	Saad et al[15]

IV=Intravenous; PO=per OS; SRE=Skeleteal-related event.

Data modified from Brown JE et al. The role of bisphosphonates in breast and prostate cancer. *Endocr Relat Cancer.* 2004; 11:207-224.

Metastatic Breast Cancer

Randomized trials comparing bisphosphonates with either placebo or no treatment in patients with breast cancer and bone metastases have shown that bisphosphonate treatment can significantly reduce or delay SREs. Results from these trials are summarized in Table 4.[12,13,15,43-49] Although all intravenous bisphosphonates reduce skeletal complications compared with placebo, intravenous pamidronate and intravenous zoledronic acid have demonstrated the most consistent clinical benefit across multiple endpoints.

Two large trials have evaluated pamidronate in patients with stage IV breast cancer. These trials, which were both 2-year multicenter randomized placebo-controlled trials, established the efficacy and safety of pamidronate 90 mg via a 2-hour infusion every 3–4 weeks for the treatment of bone metastases secondary to breast cancer. The trials involved a total of 756 patients who were receiving either chemotherapy[13] or hormonal therapy.[44] The 90-mg dose of pamidronate was significantly superior to placebo in reducing the skeletal complications of bone metastases across all endpoints in these patients.

An updated pooled analysis of these trials demonstrated that, compared with placebo, pamidronate reduced the incidence of SREs (51% vs 64%; *P*<.001), increased the time to first SRE by almost 6 months (12.7 months vs 7.0 months; *P*<.001), and reduced the skeletal morbidity rate (2.4 vs 3.7; *P*<.001).[5] Based on these results, the 90-mg dose of pamidronate administered via a 2-hour infusion was approved in the United States.

Zoledronic acid was compared with placebo in a randomized trial involving 228 Japanese women with bone metastases from breast cancer.[12] The patients in this study had predominantly osteolytic lesions. Compared with placebo, zoledronic acid significantly reduced the rate of SREs by 39% and reduced the percentage of patients with at least one SRE by 20% (29.8% vs 49.6%; *P*=.003). The median time to first fracture was not reached in the 1-year trial in the zoledronic acid group, but it was 364 days in the placebo group.

The only head-to-head comparison of two bisphosphonates in a phase III study involved zoledronic acid and pamidronate.[45] This was the pivotal trial of zoledronic acid. The trial, involving 1,648 patients with metastatic breast cancer or multiple myeloma, was designed as a noninferiority trial. It compared 24 months of treatment with zoledronic acid 4 mg or 8 mg (subsequently reduced to 4 mg) as a 15-minute infusion versus pamidronate 90 mg as a 2-hour infusion. In the subset of patients with breast cancer, zoledronic acid 4 mg was at least as effective as pamidronate 90 mg after 24 months in a comparison of the percentage of patients experiencing at least one SRE (the primary endpoint; 46% vs 49%). However, zoledronic acid reduced the overall risk of developing any skeletal complication by 20% when compared with pamidronate (relative risk=0.799; *P*=.025). Furthermore, breast cancer patients who had primarily lytic lesions had a 30% lower risk of developing SREs with zoledronic acid than with pamidronate.[6] Based on these results, zoledronic acid received broad international approval for treatment of patients with bone metastases. These results provide preliminary evidence of a differential clinical benefit favoring zoledronic acid over pamidronate.

Guidelines issued in 2003 by the American Society of Clinical Oncology (ASCO) for the treatment of bone metastases in patients with breast cancer did not consider the evidence from this study to be sufficient to recommend the use of one agent over another.[50] Thus, for breast cancer patients who have evidence of bone destruction on plain radiographs, computed tomography scan, or MRI, the guidelines allow the use of either intravenous pamidronate 90 mg delivered over 1–2 hours or intravenous zoledronic acid 4 mg administered over 15 minutes every 3–4 weeks.

Metastatic Prostate Cancer

Several bisphosphonates, including clodronate, pamidronate, and zoledronic acid, have been evaluated in patients with bone metastases secondary to prostate cancer. In placebo-controlled trials, neither clodronate (oral and intravenous) nor pamidronate 90 mg intravenously every 3 weeks showed any significant benefit on skeletal endpoints.[47,48] Zoledronic acid is the only bisphosphonate that has demonstrated a significant reduction in skeletal events in patients with advanced prostate cancer. A randomized, placebo-controlled trial involving 643 patients evaluated treatment with zoledronic acid (4 mg or 8 mg) for 15 months, followed by a 10-month extension phase.[15] At 15 months, all three major skeletal outcome parameters were significantly improved in patients receiving zoledronic acid 4 mg compared with patients receiving placebo. The 24-month results confirmed the 15-month data: the zoledronic acid 4-mg group achieved a significant reduction in the incidence of skeletal complications (38% vs 49%; *P*=.028 at 24 months) and pathologic fractures (13% vs 22%; *P*=.015 at 15 months). Zoledronic acid prolonged the time to first skeletal complication by approximately 6 months and reduced the overall risk of complications by 36%.[15,16] Based on this evidence, the FDA approved zoledronic acid for use in men with metastatic hormone-refractory prostate cancer.

Multiple Myeloma

Pamidronate 90 mg every 3–4 weeks has been widely used as palliative therapy in patients with osteolytic lesions from multiple myeloma. This dosage significantly reduced and delayed the onset of skeletal complications in a placebo-controlled trial of 392 patients with stage III myeloma.[20] After 21 cycles, the skeletal morbidity rate was reduced from 2.2 with placebo to 1.3 with pamidronate (*P*=.008).

Zoledronic acid received FDA approval for use in multiple myeloma based on the previously described randomized comparison with pamidronate in patients with lytic bone lesions from multiple myeloma or metastatic breast cancer.[51] The proportion of patients with any SRE was the same between the two treatments (44% and 46%) and did not differ between multiple myeloma and breast cancer patients.

Hypercalcemia of Malignancy

Intravenous bisphosphonate therapy, together with rehydration, has become an established treatment for hypercalcemia.[22] A single 5-minute infusion of zoledronic acid 4 mg led to faster and more sustained normalization of calcium levels than a 2-hour infusion of pamidronate 90 mg

in patients with hypercalcemia in the comparative trial of zoledronic acid versus pamidronate.[22] The 4-mg dose of zoledronic acid has received FDA approval for the treatment of hypercalcemia of malignancy and is considered first-line therapy when intravenous bisphosphonates are indicated.

Guidance on Bisphosphonate Use

Clinical practice recommendations for the use of bisphosphonates based on best available evidence have been issued by ASCO for breast cancer[50] and multiple myeloma[18] and by a multidisciplinary European expert panel for solid tumors.[52]

For patients with breast cancer or multiple myeloma who demonstrate lytic bone lesions on radiographs, computed tomography scan, or MRI, the guidelines recommend intravenous pamidronate 90 mg delivered over an interval of at least 2 hours, or zoledronic acid 4 mg delivered over 15 minutes, every 3–4 weeks. Infusion times should not be shortened because of the risk of renal toxicity with more rapid infusion.[50] No change in dosage, infusion time, or interval is required for patients with preexisting renal disease and a serum creatinine level less than 3 mg/dL, but serum creatinine should be measured before each dose of pamidronate or zoledronic acid. Bisphosphonate treatment has not been studied in patients with more severe renal dysfunction.

Data on the optimal use of bisphosphonates, including initiation of therapy and treatment duration, remain scarce. The maximum duration of use of bisphosphonates in clinical trials was approximately 24 months. Current guidelines for breast cancer recommend that treatment be continued until there is evidence of a substantial decline in a patient's performance status or the clinician determines that the likely benefit does not justify the inconvenience of receiving an intravenous drug.[50] The consequences of stopping bisphosphonate therapy after one or more skeletal events have occurred are not known. A European expert panel recommended that, because bisphosphonates continue to reduce the risk of SREs, treatment with these agents should be ongoing even after a skeletal event.[52] In the most recent update of the ASCO guidelines for multiple myeloma, the Update Committee suggests that bisphosphonate treatment continue for a period of 2 years.[53] At 2 years, physicians should seriously consider discontinuing bisphosphonates in patients who have responsive or stable disease, but the decision to continue further use is left to the discretion of the treating physician.

Despite the benefits of bisphosphonates, only a proportion of skeletal events are prevented. Additionally, some patients do not experience skeletal complications despite the presence of bone metastases. In the placebo arms of the bisphosphonate trials, approximately 50% of patients did not develop an SRE over 2 years. Because of the logistics and cost of delivering monthly intravenous infusions for all patients, there is a need to develop prediction models for the risk of skeletal events based on clinical characteristics such as type and extent of underlying disease, life expectancy of the patient, probability of experiencing an SRE, and likelihood of compliance with monthly treatment. Monitoring of biochemical markers such as NTx to identify high-risk patients and guide bisphosphonate therapy is also being actively investigated,[38] but this is not currently recommended for routine patient care.

Although there are no consensus guidelines for use of bisphosphonates in patients with prostate cancer, recent recommendations from an international expert panel suggest that bisphosphonate treatment with zoledronic acid is a reasonable option for patients with hormone-refractory metastatic disease.[52]

Prevention of Bone Metastases

The potential role of bisphosphonates in the treatment of malignant bone disease has expanded to the prevention of bone metastasis. Preclinical evidence suggests that bisphosphonates have antitumor effects, and this has led to trials examining the efficacy of bisphosphonates in the adjuvant setting, for the purpose of preventing or delaying the development of bone metastases.

Several mechanisms have been proposed to explain the antitumor effects of bisphosphonates. Bisphosphonates may inhibit tumor growth by a direct apoptotic effect on tumor cells or by an indirect effect involving inhibition of osteoclast-mediated bone resorption and reduction in the release of tumor-stimulatory growth factors from the bone matrix.[8,54] Antiangiogenic effects of bisphosphonates have also been observed and may add to their antitumor potential by decreasing microvessel density in tumor-infiltrated areas and inhibiting vascular endothelial growth factor.[8,55] Bisphosphonates also have the potential to enhance the antitumor activity of chemotherapeutic agents used in the clinical setting. For example, sequential treatment of human breast and prostate cancer cell lines with clinically relevant doses of doxorubicin followed by zoledronic acid has enhanced the degree of apoptosis over that induced by either agent alone.[56]

The antitumor efficacy of bisphosphonates in animal model systems provides a rationale for use of these agents in the early stages of cancer to slow the development of metastases. In the murine 4T1/luc breast cancer model, zoledronic acid inhibited not only metastasis to the bone but also metastasis to visceral organs such as the liver and lung.[57] A recent radiographic study of skeletal tumor growth in a mouse xenograft model of human breast cancer showed that clinically relevant doses of zoledronic acid inhibited the formation of osteolytic lesions and decreased tumor burden.[58]

Adjuvant Therapy with Bisphosphonates

Breast Cancer

Initial clinical studies investigating whether early-generation bisphosphonates can prevent bone metastases have yielded mixed results. Results from three placebo-controlled clinical trials using the relatively low-potency oral bisphosphonate clodronate in patients with primary breast cancer have been reported (Table 5).[43,54,59-62] In the largest study, 1,069 patients were randomized to receive oral clodronate 1,600 mg or placebo for 2 years.[59] Over a 5-year follow-up period, oral clodronate significantly reduced the incidence of bone metastasis (9.6% vs 13.5%; *P*=.043) and improved survival.[63] A second study, involving 302 patients, also examined 2 years of treatment with oral clodronate and initially showed a significant reduction

Table 5. The Use of Adjuvant Oral Clodronate in Primary Operable Breast Cancer*[43,54,59-62]

No. of patients	Period of clodronate treatment (yr)	Occurrence of bone metastases (clodronate vs placebo)	Occurrence of nonbone metastases	Deaths (clodronate vs placebo)	Reference
1,069	2	At 2 years: 2% vs 5% (*P*=.016) At >2 years: 10% vs 10% (*P*=.73)	At >2 years: 21% vs 24% (*P*=.26)	At 2 years: 8% vs ≈8% At 5 years: 17% vs 22% (*P*=.047)	Powles et al[59]
299	3	21% vs 17% (*P*=.27)	43% vs 25% (*P*=.009)	At 5 years: 30% vs 17% (*P*=.01)	Saarto et al[60]
302	2	14% vs 24% (*P*=.044)	16% vs 26% (*P*=.091)	At 8.5 years: 20% vs 41% (*P*=.04)	Diel et al[54,61,62]

*Average follow-up time was 4.5 to 5.5 years.

Data modified from Brown JE et al. The role of bisphosphonates in breast and prostate cancer. *Endocr Relat Cancer*. 2004; 11:207-224.

in the incidence of distal metastases (osseous and visceral), as well as an improvement in survival.[61] Although the reduced incidence of metastases and disease-free survival were not maintained, the overall survival benefit seen with clodronate was maintained with long-term follow-up in women with breast cancer.[62] A third trial, in which 299 patients were treated for 3 years, provided contradictory results, showing no significant difference in the incidence of bone metastases but a significantly higher incidence of nonskeletal metastases and a significantly shorter duration of disease-free survival in the clodronate group.[60]

The new-generation nitrogen-containing bisphosphonates have greater antiresorptive and antitumor potency and may offer greater preventive benefits in the adjuvant setting. In early clinical studies, intravenous zoledronic acid demonstrated antitumor effects when administered as adjuvant therapy in women with early-stage breast cancer. A pilot study in women with early-stage breast cancer evaluated the response of bone marrow micrometastases to treatment with intravenous zoledronic acid 4 mg every month for 2 years.[64] The presence of occult tumor cells signifies an increased risk of distal metastases and death. After 12 months of treatment with zoledronic acid, there was a significant decrease from baseline in the number of occult tumor cells (P=.0017). An antitumor effect of zoledronic acid was also noted in two large multicenter studies, the Zometa-Femara Adjuvant Synergy Trials (Z-FAST and ZO-FAST), which primarily compared the effects on bone loss associated with upfront versus delayed administration of zoledronic acid in postmenopausal women with early-stage breast cancer who were concurrently receiving letrozole.[65] At 12 months, the combined analysis of these trials showed a significantly lower rate of disease recurrence among patients who received zoledronic acid from the start (0.84% vs 1.9% in the delayed-administration group). At 36 months, the ZO-FAST trial continued to show a lower rate of disease recurrence among patients receiving early treatment (treatment difference of 9.29 [P<.0001] at the lumbar spine and 5.41 [P<.0001] at the hip).[66] Longer follow-up is required to ascertain the clinical significance of this finding. Similarly, the Austrian Breast and Colorectal Cancer Study Group Trial 12 (ABCSG-12) examined the effect of intravenous zoledronic acid 4 mg every 6 months in premenopausal breast cancer patients receiving adjuvant endocrine therapy.[67] Interim results obtained after a median follow-up of 5 years showed that endocrine therapy plus zoledronic acid significantly reduced the risk of events compromising disease-free survival by 36% compared with endocrine therapy alone (hazard ratio [HR]=0.65; P=.01). The risk of relapse-free survival events also decreased significantly among patients receiving zoledronic acid (HR=0.65; P=.015).

Prostate Cancer

Recent randomized controlled trials of bisphosphonates in men with prostate cancer and bone metastases failed to demonstrate any significant anticancer benefits. The MRC PR05 trial in men with androgen-dependent cancer, and the NCIC PR06 trial in men with androgen-independent cancer, both evaluated the use of clodronate and did not find a statistically significant improvement in disease progression or survival compared with placebo.[47,68] Similarly, an international trial failed to demonstrate any survival benefit for intravenous pamidronate given every 3 weeks for 27 weeks in comparison with placebo.[68] The inability to show a benefit with bisphosphonates in these trials could have been due to protocol variations, including the use of less potent agents, inadequate sample size, and enrollment of patients with more advanced disease.[68] In addition, these studies involved patients already diagnosed with bone metastases. Zometa 704 was designed to assess the effect of zoledronic acid on the time to first bone metastasis in men with progressive castrate, nonmetastatic prostate cancer.[69] The study was placed on hold and eventually terminated because the observed event rate was lower than expected.

Ongoing Clinical Trials

Several large ongoing studies should provide more conclusive information on the usefulness of bisphosphonates in the management of bone metastases (Table 6).[70-72] The National Surgical Adjuvant Breast and Bowel Project (NSABP)-B-34 is a 3-year trial that is comparing the effects of oral clodronate 1,600 mg/day with placebo on disease progression in 3,400 patients with stage I or II breast cancer.[70] A large three-arm, 3-year trial is being performed by the Southwest Oncology Group (SWOG) (SWOG 0307) to compare the effects of intravenous zoledronic acid (4 mg every month for 6 doses, then every 3 months), oral clodronate (1,600 mg/day), and oral ibandronate (50 mg/day) on disease-free and overall survival in patients with resected primary stage I to IIIA breast cancer; estimated accrual is 4,500 patients.[70] The potential synergy between bisphosphonates and chemotherapeutic agents is being evaluated in the 5-year Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) trial, which compares the effects of standard chemotherapy with or without intravenous zoledronic acid 4 mg (6 doses every month initially, followed by 8 doses at 3-month intervals, and then 5 doses every 6 months) on disease-free survival and bone metastasis–free survival in 3,360 women with stage II or III breast cancer. Preliminary safety analyses performed within 6 months of randomization suggest that the addition of zoledronic acid to chemotherapy is safe and does not increase myelotoxicity.[71]

Table 6. Ongoing Trials of Bbisphosphonates for Prevention of Bone Metastases in Breast and Prostate Cancer[70-72]

Trial	Treatment/Duration	Patients	Number of patients	Primary outcome
NSABP-B-34[70]	Oral clodronate 1,600 mg/day Placebo 3 years	Stage I or II breast cancer	3,400	Disease-free survival
SWOG 0307[70]	IV zoledronic acid 4 mg every month for 6 doses, then every 3 months for 2.5 years Oral clodronate (1,600 mg/day) Oral ibandronate (50 mg/day) 3 years	Resected primary stage I-IIIA breast cancer	4,500	Disease-free survival Overall survival
AZURE[71]	Chemotherapy + IV zoledronic acid 4 mg (6 doses monthly, then 8 doses every 3 months, then 5 doses every 6 months) Chemotherapy alone 5 years	Stage II or III breast cancer	3,360	Disease-free survival Bone metastasis–free survival
ZEUS[72]	Standard therapy + IV zoledronic acid 4 mg (every 3 months for 48 months) Standard therapy alone 4 years	High-risk prostate cancer and no bone disease	1,300	Proportion of patients who develop bone metastases

IV=intravenous.

Clinical trials are also investigating the potential benefits of zoledronic acid for prevention of bone metastases in men with prostate cancer. The Zoledronic Acid European Study (ZEUS) is a collaborative trial among the European Association for Urology, the Scandinavian Prostate Cancer Group, and the Arbeitsgemeinschaft Urolologische Onkologie. This phase III randomized study is investigating the efficacy of adding intravenous zoledronic acid (4 mg every 3 months for 48 months) to standard therapy in preventing or delaying bone metastases.[72] Eligible patients must have high-risk prostate cancer (PSA ≥20 ng/mL, Gleason score 8–10, and positive lymph nodes) and no bone disease.

Because of conflicting data from earlier trials, the use of bisphosphonates for the prevention of bone metastases is currently not recommended by ASCO.[50] Ongoing trials will determine the clinical usefulness of bisphosphonate therapy in patients with early breast cancer or prostate cancer. These trials should provide information on the optimal timing of therapy and type of bisphosphonate to use and criteria for identifying patients who are promising candidates for adjuvant bisphosphonate therapy.

Treatment of Bone Loss Secondary to Oncologic Therapies

In the general population, bone mass declines with age in both men and women because of decreasing estrogen levels.[73] The decline in circulating estrogen levels leads to an imbalance favoring bone resorption over new bone formation. The net effect is osteoporosis, a systemic disease characterized by low bone mass and microarchitectural disorganization that increases bone fragility and susceptibility to fracture. The National Osteoporosis Foundation has estimated that more than 10 million men and women in the United States have osteoporosis, and another 37 million have low bone mass.[74] Among individuals older than age 50, the estimated lifetime risk of developing a fracture is 40% for white women and 13% for white men.[75]

Bone Loss and Fracture Risk With Anticancer Treatments

Cancer patients are at increased risk for osteoporosis because many cancer treatments lead to an accelerated loss of bone mass. The hypogonadal state, induced by several hormonal and nonhormonal treatments, increases bone resorption and bone turnover. Estrogen depletion occurs in women treated with aromatase inhibitors or gonadotropin-releasing hormone (GnRH) agonists, and, in men, androgen-deprivation treatment (ADT) such as bilateral orchiectomy and use of GnRH agonists can cause hormone depletion that leads to skeletal fragility. Now that these treatments are being introduced earlier in the disease course, many men and women are experiencing longer periods of gonadal suppression. Cancer patients are also often treated with corticosteroids, radiation therapy, high-dose chemotherapy, and bone marrow transplantation, which are additional causes of bone loss (Table 7).[76]

Bone loss that occurs in association with cancer is generally more rapid and severe than that related to postmenopausal bone loss in women or age-related bone loss in men (Figure 1).[76] In premenopausal women, chemotherapy or GnRH agonist therapy heightens the risk for premature menopause. This can lead to rapid bone loss, with bone mineral density (BMD) loss averaging 4% after the first 6 months of therapy and an additional 3.7% over the next 6 months.[77] After ovarian ablation, up to 13% of bone mass may be lost within 1 year of treatment.[77] In postmenopausal women, endocrine therapy can deplete the already lower levels of residual estrogen that are important for maintaining BMD. Aromatase inhibi-

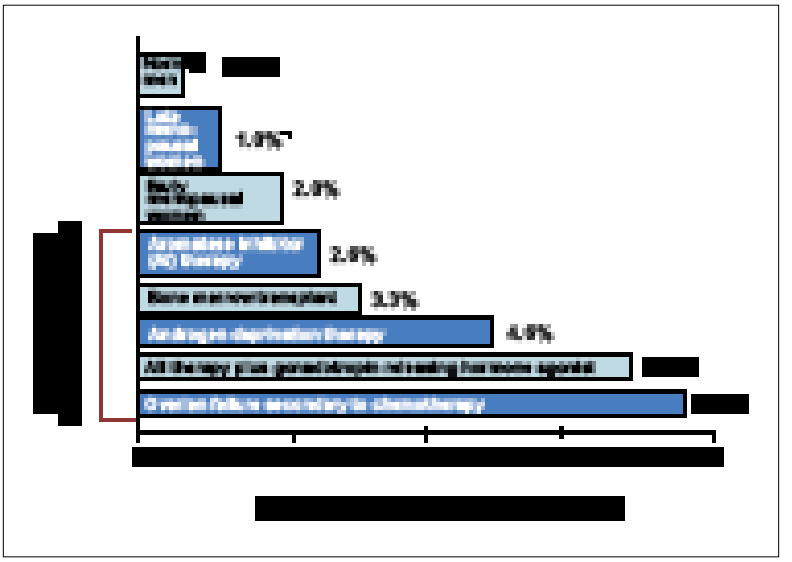

Figure 1. Bone loss associated with various cancer therapies occurs at rates that are substantially greater than those seen with normal aging in men and women.[76]

BMD=Bone mineral density

Table 7. Selected Cancer Therapies Associated with Bone Loss[76]

Therapy	Tumor
Bilateral orchiectomy	Prostate cancer
Oophorectomy	Breast cancer
Androgen deprivation therapy	Prostate cancer
Chemotherapy	Various malignancies
Cyclophosphamide	Breast cancer
Methotrexate/ifosfamide	Osteosarcoma
Alkylating agents	Hodgkin/non-Hodgkin lymphoma
Selective estrogen-receptor modulators	Breast cancer
Aromatase inhibitors	Breast cancer
Glycocorticoids/cyclosporine	Stem cell transplantation for various malignancies
Radiation therapy	Various malignancies

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tor therapy, which is increasingly the preferred adjuvant treatment in postmenopausal women with breast cancer, further increases the fracture risk. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial compared 5 years of adjuvant therapy with anastrozole, tamoxifen, or both, in postmenopausal women with early-stage breast cancer.[78] BMD measurements after 5 years showed that patients treated with anastrozole lost 8.1% and 7.4% of BMD at the lumbar spine and hip, respectively, relative to patients treated with tamoxifen. Over 5 years, fractures occurred in 11.0% of patients treated with anastrozole and 7.7% of those treated with tamoxifen.[79] The recent 100-month analysis of this trial reported an annual on-treatment fracture rate of 2.93% for anastrozole versus 1.90% for tamoxifen ($P<.0001$). However, after treatments were completed, fracture rates were comparable between the two groups.[80] Increased fracture rates were also reported for the aromatase inhibitor letrozole in the Breast International Group (BIG) 1-98 trial that compared letrozole with tamoxifen.[81] Fracture rates were 8.6% for letrozole versus 5.8% for tamoxifen ($P<.001$). It therefore appears that aromatase inhibitors are associated with high rates of bone loss and fracture.

Increasing numbers of men with prostate cancer are receiving ADT as early detection and aggressive management become the norm. A recent population-based study determined that the use of ADT in the United States rose steadily from 1.8% in 1993 to 2.9% in 2000.[82] Men with prostate cancer who are receiving ADT experience accelerated bone loss, osteoporosis, and a potential for increased rates of fracture. Advanced age, preexisting osteoporosis, and other medical conditions may heighten the risk of skeletal complications in men with prostate cancer.

A rapid loss of BMD occurs within the first 6–12 months of ADT. In one prospective study, hip and ultra distal radius BMD decreased by 3.3% and 5.3%, respectively, after 1 year of GnRH analogue therapy compared with control treatment.[83] A large database study of more than 50,000 men with prostate cancer who survived at least 5 years reported a fracture incidence of 19.4% in those who received ADT compared with 12.6% in those who did not receive ADT ($P<.001$). The risk of fracture correlated with the number of doses of ADT received during the first 12 months after diagnosis.[84] A claims-based cohort study similarly found an elevated risk for fracture in men with nonmetastatic prostate cancer who received a GnRH agonist compared with matched controls not receiving GnRH agonists (8.29 fractures vs 6.64 fractures per 100 person-years).[85]

Assessment of Fracture Risk

Osteoporosis can be diagnosed, prevented, and treated before any fracture occurs. However, bone density testing is performed in only 3–32% of high-risk patients,[76] and osteoporosis often goes unrecognized until a bone fracture occurs. Early detection and prevention of bone loss are therefore important goals of therapy. The ASCO guidelines, recognizing that many women with newly diagnosed breast cancer are at increased risk of osteoporosis because of their age or treatment, recommend that routine assessments of bone health be part of the overall management of breast cancer.[50] The guidelines provide an algorithm for the management of bone loss in breast cancer patients. Specifically, all women with nonmetastatic breast cancer should be screened for osteoporosis risk, and those at high risk should have BMD evaluated. Factors placing women at high risk include age greater than 65 years, age 60–64 years and a family history of fractures, body weight less than 70 kg, and prior nontraumatic fracture or other risk factors. Postmenopausal women receiving aromatase inhibitor therapy and premenopausal women who have experienced treatment-associated premature menopause are also considered to be at high risk.[50]

Similarly, for men with prostate cancer, the most recent NCCN clinical practice guidelines recommend baseline BMD testing for men who undergo surgical or chemical castration, particularly if long-term ADT is planned.[36]

For practical purposes, the diagnosis of osteoporosis rests on assessment of BMD as a measure of bone mass.[86] Dual energy X-ray absorptiometry (DEXA) scan of the hip and spine is the standard measurement of BMD. The World Health Organization has defined the criteria for osteoporosis and osteopenia according to DEXA scan measurements (Table 8).[2] Skeletal BMD correlates with bone strength and is predictive of fractures. Each decrease of 1 SD in BMD doubles the fracture risk.[87] However, BMD alone fails to identify many postmenopausal women who experience an osteoporotic fracture as having osteoporosis, and, conversely, fractures are not inevitable in those with low BMD. Additionally, the majority of women who have an osteoporosis-related fracture are never assessed for osteoporosis with DEXA scan. BMD is just one component of the fracture risk, and other skeletal and nonskeletal factors also contribute.[86] Recognizing the limitations of using BMD alone to predict fracture risk and the limited availability of BMD screening in many countries, the World Health Organization has developed a fracture risk assessment tool called FRAX (available at http://www.shef.ac.uk/FRAX/) that uses clinical risk factors to provide estimates of 10-year fracture incidence. The ten risk factors used in the FRAX algorithm are age, sex, prior fragility fracture after age 50, history of corticosteroid use, parental history of hip fracture, rheumatoid arthritis, secondary osteoporosis, current smoker, alcohol use, and body mass index.[74] The FRAX tool provides estimates of fracture incidence with or without BMD measurements.

Table 8. World Health Organization Criteria for Bone Loss[2]

Diagnosis	T Score
Normal	>–1.0
Osteopenia	–1.0 to –2.5
Osteoporosis	≥–2.5
Severe osteoporosis	≥–2.5 with fracture(s)

Data from Theriault RL. Pathophysiology and implications of cancer treatment-induced bone loss. *Oncology (Williston Park).* 2004 May;18(5 Suppl 3):11-15.

Treatment of Cancer Therapy–Induced Bone Loss

Currently, no treatments are approved specifically for prevention of cancer therapy-associated bone loss. In general, basic treatment options for bone loss include supplementation with calcium (at least 1,200 mg per day) and vitamin D (800–1,000 IU per day for individuals older than 50 years), weight-bearing exercise, strategies to prevent falls, and avoidance of tobacco products and excessive alcohol.[50,74] Vitamin D levels should be in the recommended range of 30–60 ng/mL for cancer patients.[88] For all men on long-term ADT, NCCN guidelines recommend supplementation with calcium (500 mg) and vitamin D (400 IU).[36]

Several pharmacologic therapies have been approved for prevention or treatment of non–cancer-related osteoporosis, including oral and intravenous bisphosphonates, estrogen or hormone therapy, raloxifene, calcitonin, and parathyroid hormone.[74] However, hormone therapy, raloxifene, and parathyroid hormone have drawbacks that make them unsuitable for use in breast cancer patients. ASCO guidelines recommend bisphosphonate therapy for breast cancer patients whose BMD measurement is indicative of osteoporosis, defined as a T score –2.5 or lower (Figure 2).[50] For men who are osteopenic or osteoporotic, NCCN guidelines recommend that bisphosphonate therapy with zoledronic acid, pamidronate, or alendronate, or treatment with the selective estrogen-receptor modulators (SERMs) raloxifene or toremifene, be considered.[36]

Preservation of Bone Density in Breast Cancer

Bisphosphonates may be used in conjunction with chemotherapy or endocrine therapy. Alendronate, risedronate, ibandronate, and zoledronic acid are approved in the United States for prevention or treatment of non–cancer-related osteoporosis. Studies of these and other bisphosphonates demonstrate a beneficial effect on inhibiting bone loss and, in some cases, on reducing the fracture risk.[74] Once-weekly oral risedronate or daily oral clodronate administered for 24 months reduced the loss of BMD in women receiving treatment for breast cancer.[89,90] None of the patients in the clodronate study and fewer than 50% of the patients in the risedronate study were receiving aromatase inhibitors.

Four large studies have been designed to evaluate the use of intravenous zoledronic acid for the prevention of bone loss in patients with early breast cancer who are receiving aromatase inhibitor therapy: ABCSG-12, Z-FAST, ZO-FAST, and E-ZO-FAST. The ABCSG-12 trial was conducted in premenopausal women receiving adjuvant endocrine therapy (goserelin plus tamoxifen or anastrozole) with or without zoledronic acid 4 mg every 6 months for 3 years[91] Bone loss after treatment with anastrozole was more severe than that associated with tamoxifen after 3 years (BMD loss, 17.3% vs 11.6%). Treatment with zoledronic acid stabilized BMD and decreased the proportion of patients who met the criteria for overt osteoporosis from 22% to 1% after 3 years of

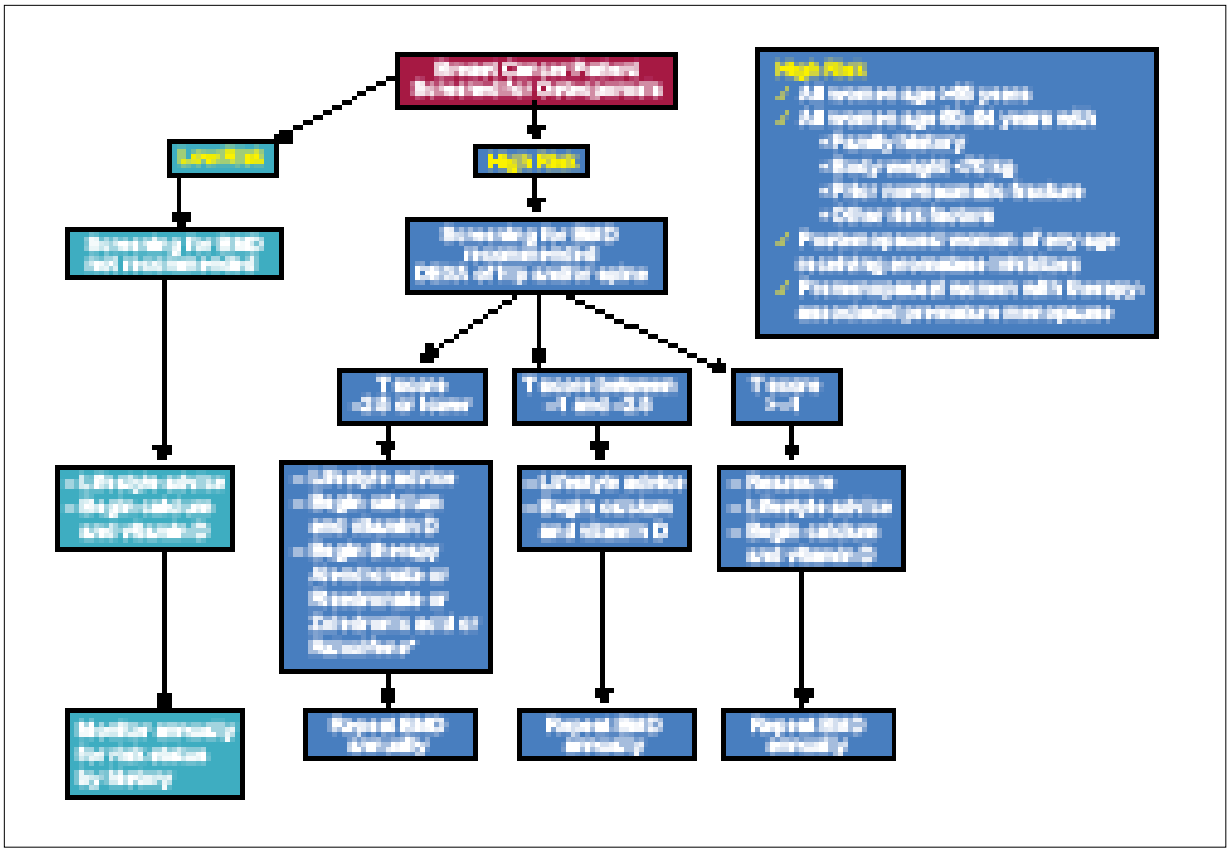

Figure 2. Recommended management strategy for patients with diagnosed nonmetastatic breast cancer. This management strategy is largely based on influence from results in non–breast cancer populations.[50]

Hillner BE et al. *J Clin Oncol.* 2003;21(21):4042-4057.

therapy. At the 5-year follow-up, BMD remained stable in patients who had been assigned zoledronic acid therapy during the 3 years of treatment, and it increased during the 2 years following completion of therapy; in contrast, patients receiving endocrine therapy alone did not recover their baseline BMD levels.[92]

Additional evidence for the efficacy of zoledronic acid comes from the three companion trials Z-FAST, ZO-FAST, and E-ZO-FAST in postmenopausal women. These 5-year trials are determining whether upfront or delayed therapy (after a fracture or BMD T score decrease to –2.0) with intravenous zoledronic acid (4 mg every 6 months) can decrease BMD losses in women receiving adjuvant letrozole. At 12 months, among patients who received immediate treatment with zoledronic acid, lumbar spine BMD and total hip BMD measurements were 4.4% and 3.3% higher, respectively, than in the delayed-administration group.[93] An integrated 12-month analysis of data from Z-FAST and ZO-FAST has confirmed these preliminary findings in a larger number of patients, showing that upfront zoledronic acid can prevent aromatase inhibitor–induced bone loss in early-stage breast cancer patients.[65] At 36 months, the ZO-FAST trial continued to show a lower rate of bone loss among patients receiving early treatment (treatment difference of 9.29 [P<.0001] at the lumbar spine and 5.41 [P<.0001] at the hip).[66] Fracture rates did not differ between the upfront and delayed-administration groups during the first 36 months. Long-term outcomes from these trials are awaited, but the early results of these trials suggest that initiation of zoledronic acid treatment before the occurrence of a fracture or severe osteoporosis may prevent or delay bone loss in postmenopausal women receiving aromatase inhibitors.

Preservation of Bone Density in Prostate Cancer

Several studies have reported that bisphosphonates preserve bone density in men with prostate cancer. However, most of the studies were insufficiently powered to evaluate the risk of fractures. In an open-label study, intravenous pamidronate (60 mg every 12 weeks) prevented bone loss at the hip and lumbar spine in men with advanced or recurrent prostate cancer receiving a GnRH agonist.[94] Mean trabecular BMD of the lumbar spine decreased by 8.5% in men receiving leuprolide alone, but it did not change in men who also received pamidronate. By contrast, once-weekly treatment with oral alendronate (70 mg) for 1 year in men receiving ADT significantly increased BMD of the spine by 3.7% and of the hip by 1.6%, and it reduced markers of bone turnover, compared with treatment with calcium and vitamin D alone, which resulted in a loss of BMD.[95]

In men starting ADT, intravenous zoledronic acid (4 mg every 3 months for 1 year) increased BMD in the lumbar spine by 5.6%, compared with a 2.2% decrease in men taking placebo.[96] BMD also increased in the femoral neck, trochanter, and total hip with zoledronic acid treatment. Delaying the initiation of zoledronic acid until 6–12 months after beginning ADT also prevented bone loss and resulted in an increase in BMD that was similar to that obtained in the study just described, in which bisphosphonate therapy was begun upon initiation of ADT.[97] Another randomized study showed that the effects of a single treatment of zoledronic acid on BMD and bone turnover were comparable to those observed with zoledronic acid given every 3 months, which suggests that an annual infusion of zoledronic acid may be sufficient to prevent treatment-related bone loss.[98]

SERMs such as raloxifene and toremifene may be useful for mitigating the bone loss accompanying GnRH agonist therapy. In men with prostate cancer treated with raloxifene (60 mg daily) for 12 months, hip BMD increased by 1.1%, compared with a decrease of 2.6% in men treated with placebo.[99] There was a trend toward an increase in spinal BMD with raloxifene. An ongoing 24-month, multicenter fracture-prevention study is evaluating the efficacy of toremifene (80 mg daily), a second-generation SERM, for prevention of morphometric vertebral fractures in men with prostate cancer receiving ADT. After 1 year of treatment, patients who received toremifene, compared with the placebo group, had significant increases in BMD at each evaluated skeletal site (lumbar spine, 1.6% vs –0.7%; total hip, 0.7% vs –1.3%; femoral neck, 0.2% vs –1.3%).[100]

Toxicities Associated with Bone-Targeted Therapy

The adverse events associated with bisphosphonate therapy are mainly mild to moderate in nature. The most common adverse events associated with administration of intravenous bisphosphonates are self-limiting flu-like symptoms such as the fever, myalgia, and arthralgia related to an acute-phase reaction. Approximately 15–30% of patients experience these symptoms, which usually occur only after the first infusion and typically resolve over 48–72 hours. These reactions can be managed with preventive or therapeutic analgesics such as acetaminophen or ibuprofen.[52]

Patients with mixed or sclerotic bone lesions, in which there is high bone turnover, who were treated with first-generation bisphosphonates, often became hypocalcemic. This has not been typically observed with second- and third-generation bisphosphonates. Although clinically relevant hypocalcemia is now rare with bisphosphonate treatment, administering calcium and vitamin D from the start may prevent this condition.[52]

Effects on Renal Function

Decreased renal function is a less common but potentially serious adverse event that may occur after the administration of intravenous bisphosphonates. In the phase III comparative trial of zoledronic acid and pamidronate, approximately 10% of patients in both groups showed a deterioration of renal function.[101]

Renal monitoring guidelines have been established to minimize the risk of renal deterioration during bisphosphonate therapy.[18,50] Adherence to the recommended infusion times is advised, and more rapid delivery of the bisphosphonate should be avoided to prevent renal toxicity. Although the safety of bisphosphonates in patients with serum creatinine levels greater than 3.0 mg/dL has not been evaluated, patients with milder renal damage (creatinine <3.0 mg/dL) can receive bisphosphonates at the recommended dosage, infusion time, and interval. The guidelines recommend measurement of serum creatinine levels at baseline and before administering any bisphosphonate infusion. The drug should be withheld from any patient who has unexplained renal dysfunction (defined as an increase of ≥0.5 mg/dL in serum creatinine or an absolute value of ≥1.4 mg/dL in a patient with normal baseline creatinine levels) until renal function recovers to baseline levels. Guidelines for patients with multiple myeloma recommend that patients receiving intravenous pamidronate or zoledronic acid be evaluated intermittently for albuminuria (defined as >500 mg/24 hours of urinary albumin) and azotemia (defined as an increase of ≥0.5 mg/dL in serum creatinine or an absolute value of ≥1.4 mg/dL in a patient with normal baseline creatinine levels). The drug should be discontinued in patients experiencing either of these conditions but may be reinstated when renal function returns to baseline. To avoid renal toxicity with intravenous bisphosphonates, patients must be adequately hydrated before treatment.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) is characterized by exposed bone within the oral cavity and has been associated with bisphosphonate therapy. ONJ is often associated with pain, infection, and soft-tissue ulceration. The true incidence of ONJ associated with bisphosphonate use has been difficult to determine because of inconsistent definitions and varied methods of data collection. The potential risk of ONJ in cancer patients receiving bisphosphonates is 1–10%.[102] A large chart review at the M.D. Anderson Cancer Center recently estimated the incidence of ONJ to be 0.73% among approximately 4,000 patients treated with intravenous bisphosphonates.[103] Most of the affected patients had either breast cancer (1.2%) or multiple myeloma (2.4%). Similarly, a systematic review of 368 patients with bisphosphonate-associated ONJ found that patients with breast cancer or multiple myeloma represented 85% of published cases of ONJ, and 94% of the affected patients had received therapy with pamidronate or zoledronic acid.[104] The potential risk of ONJ after routine oral bisphosphonate therapy for osteoporosis is low, in the range of 1 of every 10,000 to 1 of every 100,000 patients.[102]

The potential risk of ONJ increases with the potency of the bisphosphonate, the dose, and the treatment duration. In patients with breast cancer or multiple myeloma, the potential to develop ONJ has been found to be related to a longer duration of treatment and greater cumulative dose of pamidronate or zoledronic acid.[102] The mean time

to onset of ONJ in patients treated with zoledronic acid was 18 months, compared with 39–72 months in those treated with pamidronate. The faster onset with zoledronic acid treatment may reflect the higher potency of this compound. Invasive dental procedures and periodontal disease are significant potential risk factors for ONJ in breast cancer and multiple myeloma patients.[103,105] Older age at diagnosis of multiple myeloma is also a potential risk factor for ONJ.[105] Other potential factors that may predispose to the development of ONJ include the use of glucocorticoids, chemotherapy, bevacizumab, thalidomide, and tobacco, as well as the presence of comorbid conditions such as diabetes or peripheral vascular diseases.[104,106-108] These associations with ONJ require further investigation.

Because ONJ causes pain, dysfunction, and disfigurement and is difficult to treat, the focus of care is on prevention. Dental infection and dentoalveolar surgery should be avoided during bisphosphonate therapy. Patients about to begin bisphosphonate therapy should have a thorough dental examination, and any dental disease should be treated before bisphosphonate therapy is initiated. During therapy, patients should follow a rigorous routine dental care program. Established ONJ is best managed through conservative procedures such as the use of antibiotics and chlorhexidine mouth rinses, but if surgical treatment is necessary, it should be conservative or delayed. Temporary discontinuation of bisphosphonate therapy has been suggested, but no published data have established that this will promote resolution of ONJ.[102] Approximately 60% of cases of ONJ resolve regardless of continuation or discontinuation of bisphosphonates.[109] Although ONJ remains a concern, its frequency has been reduced with careful pretreatment, dental assessment, and avoidance of invasive dental procedures. For patients with bone metastases, the decision to discontinue bisphosphonates because of the potential risk of ONJ must be balanced against the considerably higher risk for SREs and their associated morbidity and mortality.

Emerging Therapies for Cancer-Related Bone Complications

Although intravenous bisphosphonates effectively treat and prevent complications from bone metastases, not all patients respond to treatment. Renal toxicity may also limit the use of bisphosphonates in some patients. New bone-directed therapies have evolved from an improved understanding of the pathogenesis of bone metastases, particularly the interactions between tumor cells and the bone marrow microenvironment. Of the several agents being explored, many are in early phases of development, but two, including denosumab and atrasentan, are currently in phase III trials. A partial list of bone-directed agents in development is shown in Table 9.

RANK-RANKL Inhibitor (Denosumab)

RANK, RANKL, and osteoprotegerin are a triad of molecules that regulate the maturation, differentiation, and survival of osteoclasts. RANKL is a key mediator in the perpetuating cycle of bone destruction in metastatic cancer. Denosumab, a humanized monoclonal antibody that binds and neutralizes RANKL, is being studied across a range of conditions, including osteoporosis, treatment-induced bone loss, bone metastases, multiple myeloma, and rheumatoid arthritis.

A randomized, active-controlled, phase II study in patients with breast cancer–related metastases showed that denosumab administered subcutaneously every 4 weeks or every 12 weeks was as effective as intravenous bisphosphonates (pamidronate, zoledronic acid, or ibandronate) in suppressing bone turnover, as measured by levels of urinary NTx at 13 weeks.[110] This trial was not designed to compare SREs in the treatment groups, but the time to first SRE was similar for patients in the denosumab and bisphosphonate cohorts, with SREs occurring in 9% and 16% of patients treated with denosumab or bisphosphonates, respectively. Another randomized, controlled, multicenter study compared the antiresorptive effects of a single dose of subcutaneous denosumab (0.1, 0.3, 1.0, or 3.0 mg/kg) or intravenous pamidronate (90 mg) in patients with multiple myeloma or breast cancer who had radiologically

Table 9. Approaches to Treating Bone Metastases

Therapy	Mechanism of action
Bisphosphonates	Inhibit osteoclast function and prevent bone resorption
Denosumab	Monoclonal antibody that inhibits RANKL-RANK interaction
Odanacatib	Cathepsin K inhibitor that prevents breakdown of extracellular matrix
Atrasentan	Endothelin receptor antagonist that inhibits osteoblast function
Src inhibitors	Inhibit bone resorption, stimulate osteoblast proliferation
Anti-DKK1 antibodies	Neutralize DKK1 activity and promote Wnt signaling and osteoblast differentiation
Bortezomib	Proteasome inhibitor that stimulates osteoblast function
Integrin antagonists	Inhibit attachment of osteoclasts to bone matrix and prevent bone resorption

DKK1=dickkopf-1; RANK=receptor activator of nuclear factor κB; RANKL=receptor activator for nuclear factor κB ligand.

confirmed bone lesions.[111] A single subcutaneous dose of denosumab reduced levels of serum or urinary NTx within 1 day in both types of cancer. The magnitude of NTx decrease was similar for the 2 treatments but was more sustained (84 days) with denosumab.

Several phase III studies are evaluating the efficacy of denosumab in metastatic bone disease. Trials in hormone-refractory prostate cancer (N=1,850), advanced breast cancer (N=1,400), and other solid tumors or multiple myeloma (N=1,700) are comparing the efficacy of denosumab with that of zoledronic acid in reducing SREs. A large placebo-controlled trial is examining whether denosumab can influence disease progression in men with hormone-refractory prostate cancer who do not yet have bone metastases (N=1,400); the primary endpoint is time to first occurrence of bone metastasis or death from any cause.[112]

The ability of denosumab to mitigate treatment-induced bone loss has been studied in a randomized, placebo-controlled trial in patients with nonmetastatic breast cancer and low bone mass (excluding osteoporosis) receiving aromatase inhibitor therapy.[113] Denosumab (60 mg subcutaneously) or placebo was administered every 6 months for 2 years. At 12 and 24 months, spinal BMD had increased by 5.5% and 7.6%, respectively, with denosumab compared with placebo (P<.0001 at both time points). Markers of bone turnover were also decreased. Increases in BMD were noted as early as 1 month after therapy began, and the degree of improvement was not influenced by the duration of aromatase inhibitor therapy. A phase III placebo-controlled trial is evaluating denosumab in the control of bone loss in 1,400 patients with nonmetastatic prostate cancer undergoing ADT.

Cathepsin K Inhibitors (Odanacatib)

Cathepsin K is a cysteine protease that is selectively expressed in and secreted by osteoclasts. It breaks down collagen, leading to resorption of bone matrix. Inhibitors of cathepsin K suppress bone resorption in animal models.[9] When administered weekly for 2 years to postmenopausal women with low BMD, a 50-mg dose of odanacatib increased spinal and hip BMD by 5.5% and 3.2%, respectively, whereas BMD remained relatively unchanged in placebo-treated subjects. Levels of urinary NTx and bone-specific alkaline phosphatase also decreased, by 52% and 13%, respectively, with odanacatib, whereas urinary NTx decreased by only 5% and bone-specific alkaline phosphatase increased by 3% with placebo.[114] A recent double-blind study showed that daily administration of odanacatib (5 mg) or zoledronic acid (4 mg) to women with metastatic bone cancer reduced markers of bone remodeling after 4 weeks. Odanacatib and zoledronic acid suppressed urinary NTx by 77% and 73%, respectively, and suppressed urinary deoxypyridinoline by 30% and 52%, respectively. Odanacatib increased serum cross-linked C-terminal peptide of type 1 collagen by 93%, indicating specific inhibition of cathepsin K.[115]

Endothelin Receptor Antagonists (Atrasentan)

Endothelin-1 (ET-1) binds to its receptor ET_A and initiates signaling pathways that play a central role in the osteoblastic response in metastatic prostate cancer. Atrasentan is an inhibitor of the ET_A receptor that has been shown to block formation of osteoblastic metastases in mice.[116] In a placebo-controlled phase II trial in men with asymptomatic hormone-refractory prostate cancer and evidence of metastasis, atrasentan significantly delayed the time to disease progression compared with placebo, in the evaluable but not the intention-to-treat population.[117] However, in a subsequent placebo-controlled phase III trial in 809 men with metastatic prostate cancer, atrasentan (10 mg/day) did not reduce the risk of disease progression relative to placebo, although levels of bone alkaline phosphatase and PSA were significantly reduced.[118] A similar placebo-controlled phase III study of atrasentan conducted in men with nonmetastatic prostate cancer but with increasing PSA levels also showed that the time to progression did not differ significantly between atrasentan and placebo treatment.[119] Combination of atrasentan with zoledronic acid in men with metastatic

prostate cancer did not induce any additive or synergistic effects on levels of alkaline phosphatase.[120]

Other Therapeutic Approaches

c-Src is a nonreceptor tyrosine kinase that may be required for the formation of the ruffled border in osteoclasts and is therefore important for the resorptive activity of these cells. Preclinical studies have demonstrated that reduction of c-Src expression not only inhibited bone resorption but also stimulated osteoblast proliferation and bone formation.[121] The c-Src inhibitor currently in clinical trials is AZD0530, an orally active small-molecular-weight inhibitor of c-Src and BCR-Abl, whose efficacy in bone resorption has been demonstrated in 2 phase I clinical trials of healthy male volunteers.[122]

TGF-β is a cytokine that promotes invasion and metastasis of human cancers through inactivation or mutations in various components of its signaling pathway. The TGF-β signal is transduced through 2 transmembrane receptors, TβRI and TβRII. Several small molecules that inhibit TβRI activity in vitro have been developed. In an experimental model of breast cancer–induced bone metastasis in mice, an inhibitor of this receptor reduced the incidence of widespread early skeletal metastases and also reduced the tumor burden, demonstrating that abrogation of TGF-β signaling in vivo could inhibit bone metastases.[123]

In some cancers, such as in multiple myeloma, osteoblastic bone formation becomes inhibited and therefore tips the balance in bone metastases toward osteolysis. Multiple myeloma cells secrete DKK1, an inhibitor of Wnt signaling that prevents osteoblast differentiation and suppresses bone formation.[31] Therapies that neutralize DKK1 activity may thus help rebuild bone. To test this concept, neutralizing anti–DKK1 antibody was injected daily in a mouse xenograft model for human primary myeloma.[124] This treatment increased BMD in the treated mice, increased osteoblast activity, reduced the number of osteoclasts, and reduced the myeloma burden.

Bortezomib is a first-in-class proteasome inhibitor, currently clinically available, that has demonstrated antineoplastic activity in multiple myeloma. In addition to its antitumor effects, bortezomib may also have a beneficial effect on bone disease. Bortezomib induces the differentiation of mesenchymal cells into osteoblasts, resulting in new bone formation. Bortezomib can increase the expression of bone-formation markers and the number of osteoblasts in biopsy specimens, but it does not affect osteoclastic activity or lytic bone disease. It has potential utility in combination with agents that target the osteolytic process.[32,125]

Another strategy for treating bone disease is to target integrins, which are receptors that anchor osteoclasts to the bone matrix and provide the physical juxtaposition needed for resorption. The αVβ3 integrin is essential to the resorptive process. In a preclinical study in rats, blockade of this receptor with a small-molecule inhibitor attenuated osteoclast activity and prevented loss of trabecular bone after oophorectomy, demonstrating the bone-sparing efficacy of this approach.[29]

Conclusions

Skeletal complications from bone metastases remain an important problem in patients with advanced cancer. Intravenous bisphosphonates are an accepted standard of practice in breast and prostate cancer patients who have bone metastases and in patients with multiple myeloma. Despite the integration of bisphosphonates into general practice, a number of questions remain regarding their optimal use. These include selection of patients for treatment, timing and duration of treatment, frequency of administration, and course of action when patients continue to have progressive bone disease. The validation of bone resorption markers may help stratify patients who will benefit from aggressive or conservative treatment and may help tailor bisphosphonate therapy to individual needs.

Of particular interest are recent preclinical and clinical findings suggesting that bisphosphonates may have antineoplastic activity and thus may prevent bone metastases. This opens up the potential for bisphosphonates to be useful in patients at earlier stages of their disease. Although clinical data are limited regarding the efficacy of bisphosphonates for preventing tumor metastasis to bone, the results from several ongoing large studies should provide conclusive information on their use as therapeutic adjuvants in patients with nonmetastatic breast or prostate cancer.

Patients who have cancer are also at significant risk for bone loss and fracture from therapy for their malignancy. In particular, estrogen- and androgen-ablative therapies, which are being used increasingly in patients with breast or prostate cancer, cause a rapid decline in bone density, leading to serious clinical consequences. Because of low awareness of this problem, significant bone loss may already be present before osteoporosis is diagnosed or a fracture occurs. Cancer therapy–associated bone loss is largely preventable. Thus, preservation of bone density must be considered an integral component of cancer therapy. Despite the growing recognition of this problem, there are currently no therapies approved specifically for preventing bone loss in patients receiving adjuvant therapy for breast or prostate cancer. Intravenous bisphosphonates, particularly zoledronic acid, are promising agents for preventing bone loss caused by cancer treatment.

Research into the pathophysiology of cancer-induced bone disease has identified new pathways and molecular interactions within the bone microenvironment that may facilitate the growth and progression of bone metastases. This knowledge has led to the development of new bone-directed therapies that target these pathogenetic mechanisms and that can potentially be used to treat metastatic disease, as well as cancer treatment–related bone loss. Inhibitors of the RANKL-RANK signaling pathway have provided promising early results and are being tested in large clinical trials. These and other biologic agents may be valuable treatment options for bisphosphonate-refractory bone metastases and may also have synergies with other bone-specific therapies and chemotherapeutic agents.

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New Opportunities for the Management of Cancer-related Bone Complications

Posttest Questions

Please select the best answer, and indicate your reponse on the answer sheet on the following page.

1. Which of the following conditions is/are most consistent with the finding of osteoblastic lesions?

a. Breast cancer
b. Prostate cancer
c. Multiple myeloma
d. Osteoporosis
e. All of the above

2. Which of the following is not typically defined as a skeletal-related event in clinical trials?

a. Spinal cord compression
b. Pathologic fracture
c. The need for radiation therapy to bone
d. Cauda equina syndrome
e. Bone pain

3. What percentage of patients with advanced lung cancer has evidence of bone metastasis?

a. 10% to 20%
b. 30% to 40%
c. 50% to 60%
d. 70% to 80%

4. All of the following therapies are associated with accelerated bone loss except

a. Hormonal deprivation
b. Radiation therapy
c. Glucocorticoids
d. High-dose chemotherapy (eg, cyclophosphamide, methotrexate)
e. All of these therapies are associated with bone loss

5. Which of the following is not increased by activation of RANK by its ligand?

a. Osteoclast maturation/differentiation
b. Osteoclast activation
c. Osteoclastic resorption
d. Osteoclast apoptosis

6. What is the most common complication seen in patients with metastasis to bone?

a. Hypercalcemia
b. Pathologic fracture
c. Pain
d. Spinal cord compression

7. Intravenous bisphosphonate therapy at higher doses and with shorter infusion times can result in

a. Cardiovascular compromise
b. Prolonged bleeding times
c. Liver toxicity
d. Renal toxicity
e. Pancreatitis

8. All of the following are potential risk factors for osteonecrosis of the jaw except

a. Multiple myeloma
b. Younger age
c. Concomitant use of thalidomide
d. Use of zoledronic acid

9. Bone scans are not recommended for

a. Prostate cancer patients treated with radiotherapy who later develop a rising PSA level
b. Post–radical prostatectomy patients who develop an undetectable PSA level that becomes >0.3 ng/mL and rises on two or more determinations
c. Symptomatic breast cancer patients with stage I or II disease
d. Multiple myeloma patients

10. What is the most common adverse event seen in patients treated with intravenous bisphosphonates?

a. Acute-phase reactions
b. Osteonecrosis of the jaw
c. Renal disease
d. Liver toxicity

Activity Evaluation Form:

Release date: May 2009 **Expiration date:** May 31, 2010

Participants requesting credit must read the CME activity. Certificates will be issued only upon receipt of completed activity posttests, along with a completed evaluation and certificate information form.

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Signature _____

✹ I would like to receive information about future educational activities on the topic of cancer-related bone complications.

(Evaluation continues on the following page.)

POSTTEST ANSWER SHEET

Please fill in your answers to the right: 1____ 2____ 3____ 4____ 5____ 6____ 7____ 8____ 9____ 10____

EVALUATION

1. Rate the extent to which you agree or disagree.	**Strongly Agree**				**Strongly Disagree**
• I am satisfied with the overall quality of this activity.	5	4	3	2	1
• Participation in this activity changed my knowledge/attitudes.	5	4	3	2	1
• I will make a change in my practice as a result of participation in this activity.	5	4	3	2	1
• The activity presented scientifically rigorous, unbiased, and balanced information.	5	4	3	2	1

Please list the changes you plan on making in your practice as a result of your participation in this activity. _____

_____

If you felt the activity was biased, please explain. _____

_____

2. This activity helped me to achieve the following objectives:	**Strongly Agree**				**Strongly Disagree**
• Recognize the clinical impact of bone metastases with respect to skeletal-related events.	5	4	3	2	1
• Summarize the pathophysiology of bone metastasis.	5	4	3	2	1
• Describe the current standard for the treatment and prevention of skeletal-related events in patients with cancer that has metastasized to the bone.	5	4	3	2	1
• Assess the risks and benefits associated with current therapies for bone metastasis.	5	4	3	2	1
• Evaluate the clinical data on the appropriate use of novel agents in development for the prevention and treatment of bone metastases as well as the prevention and treatment of bone loss secondary to oncologic therapies.	5	4	3	2	1
• Compare and contrast the mechanisms of actions of bisphosphonates and novel bone-targeting agents.	5	4	3	2	1

If you felt the learning objectives were not met, please explain. _____

_____

3. What information remains unclear? _____

_____

4. Questions or comments regarding this activity _____

_____

5. How did you hear about this activity? (Please check all that apply.)

✹ Direct mailing ✹ Curatio Web site ✹ Colleague

✹ Other (Please specify.) _____

6. Time spent completing this activity

✹ < 1 hr ✹ 1–1.5 hr ✹ 1.5–2 hr ✹ >2 hr

7. Suggested topics and/or speakers you would like for future programs: _____

_____

8. What is/are your preferred format(s) for earning continuing medical education credits? (Please check all that apply.)

✹ Satellite symposium ✹ Grand rounds ✹ CD-ROM ✹ Dinner meetings ✹ Internet activities ✹ Podcast

✹ Teleconference ✹ Journal supplement ✹ Newsletter/monograph

✹ Other (Please specify) _____