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Improving the Management of Cancer-Related Bone Complications

Introduction

Despite the fact that painful bone metastases have been a problem for as long as patients have been diagnosed with cancer, the clinical consequences of bone metastases remain underappreciated and undertreated.¹ New insights into the cellular and molecular mechanisms of bone metastasis have yielded a wealth of information and enhanced opportunities for treatment of bone metastasis and optimization of underlying bone health.

This is the first of two newsletters discussing current concepts in bone metastasis. This article reviews the epidemiology of bone metastases and the pathophysiology of malignancy-related bone complications, including interactions between cancer and the bone microenvironment. It discusses the diagnosis and management of bone metastases using currently available treatment options, examining the controversies and toxicities associated with these therapies. The second newsletter will review information regarding emerging therapies and the prevention of bone metastasis as well as the management of bone loss secondary to oncologic therapies.

The content of this newsletter is based on discussions that occurred during the **Clinical Perspectives in Cancer-Related Bone Complications** Expert Roundtable held August 4, 2008, in Philadelphia, Pennsylvania. The roundtable committee consisted of the following physicians:

- *Allan Lipton, MD (Chair)*, Professor of Medicine & Oncology, Milton S. Hershey Medical Center, Hershey, Pennsylvania
- *Gordon A. Brown, DO*, Assistant Clinical Professor of Urology, University of Medicine and Dentistry of New Jersey, Stratford, New Jersey
- *Gregory R. Mundy, MD*, Professor of Medicine, Pharmacology, Orthopedics, Cancer Biology, Vanderbilt University Medical Center, Nashville, Tennessee
- *G. David Roodman, MD, PhD*, Professor of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
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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 the understanding of the complex interaction of cancer cells with their microenvironment, and of the pathophysiologic processes involved in bone metastases, are spurring the development of novel therapeutic options for these patients. Current treatments are aimed at lessening the consequences of bone metastases once they have occurred. Novel therapies directed toward cancer cell–signaling mechanisms and the tumor microenvironment itself are being developed. Such therapies may retard the development of metastatic disease, as well as provide additional therapeutic options for managing ongoing bone loss resulting from commonly employed oncologic therapies.

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 to the bone or has the propensity for bone metastasis.

Learning Objectives

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

- Explain the clinical impact of bone metastases with respect to skeletal-related events
- Describe the pathophysiology of bone metastasis
- Summarize the current standards 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

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Improving the Management of Cancer-Related Bone Complications

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Medium

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- Active Internet connection
- Adobe Acrobat Reader

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The Impact of Bone Metastasis

Who will experience bone metastases?

Tumor metastasis to the skeleton affects more than 400,000 individuals in the United States annually and is the third most common site of metastases of solid tumors after the liver and the lung.^{2,3} By virtue of the hematologic spread of most malignancies, highly vascularized skeletal structures are most often affected, particularly the pelvis and hips, vertebrae, and ribs. The appendicular areas are less commonly involved.³

The solid tumors associated with the highest prevalence of bone metastases are advanced breast cancer and prostate cancer (Table 1).⁴ In fact, nearly 80% of patients with advanced breast or prostate cancer will eventually develop bone metastases. Other solid tumors with a propensity to metastasize to bone include melanoma and cancers of the thyroid, lung, kidney, and bladder, although the prevalence of bony involvement in these diseases is closer to 30% to 40%.^{3,4}

Table 1. Prevalence of metastatic bone disease in patients with solid tumors.⁴ Reprinted with permission of Alphamed Press, Inc., from Bisphosphonates: clinical experience, Coleman, RE, *Oncologist*, vol. 9, 2004; permission conveyed through Copyright Clearance Center, Inc.

Tumor Type	5-Year Worldwide Prevalence (1000 ×)	Incidence of Bone Metastases in Patients With Advanced Metastatic Disease (%)	Median Survival From Diagnosis of Bone Metastases (months)
Breast	3,860	65–75	19–25
Prostate	1,555	65–75	12–53
Lung	1,394	30–40	6–7
Bladder	1,000	40	6–9
Renal cell	480	20–25	12
Thyroid	475	60	48
Melanoma	5,533	14–45	6

With regard to hematologic malignancies, bone involvement is most prominent with multiple myeloma. Bone-related symptoms are the most common presenting signs of this disease. By contrast, bone involvement is uncommon in lymphomas and leukemias.³

How many patients with bone metastases will experience a skeletal-related event if left untreated?

Skeletal-related events (SREs) associated with bone metastases involve a range of complications, including impaired mobility, hypercalcemia, pathologic fracture, spinal cord or nerve root compression, bone marrow infiltration, and pain requiring surgery, radiotherapy, or opioid analgesics.

Patients with advanced breast cancer have the highest incidence of SREs, with approximately 70% experiencing at least one skeletal complication during a 2-year follow-up period.⁵ Patients with myeloma, prostate cancer, and lung cancer are also at high risk of skeletal complications. Approximately 50% of patients with these tumor types experience an SRE during a 21- to 24-month period. The most common events in all tumor types are pathologic fracture and bone pain requiring radiation.⁵ Moreover, patients with bone metastasis often experience multiple SREs, with each succeeding event occurring at a shorter interval following the initial event.⁵

What are the other clinical and economic implications of bone metastases?

SREs are an independent predictor of poor prognosis. In one study of men with prostate cancer, median overall survival was 121 and 160 months in men with and without a history of skeletal fracture since the time of their cancer diagnosis, respectively.⁶ In that study, a history of skeletal fracture was associated with a 7.4-fold increased risk of poor survival. Saad and colleagues performed a retrospective analysis of the effect of pathologic fractures on survival in 3,049 patients with multiple myeloma or solid tumors (eg, breast, prostate, or lung cancer) using a Cox regression model.⁷ Patients with multiple myeloma had the highest fracture incidence (43%), followed by patients with breast (35%), prostate (19%), and lung cancer (17%). In all tumor types except lung, pathologic fracture was associated with a significant increase in the risk of death. The increase in risk was greatest among breast cancer patients, who had a 32% increased risk of death relative to patients without a fracture (hazard ratio = 1.32; $P < .01$). By contrast, patients with multiple myeloma or prostate cancer and fracture had a >20% increased risk of death. Table 1 summarizes expected survival in patients with bone metastases across a range of solid tumor types.

SREs are generally associated with impairments in health-related quality of life, including worse physical and functional well-being, social functioning, and ability to perform basic functions of daily living, as well as an increased risk of depression and anxiety.⁵

Because of the morbidity associated with SREs, they substantially increase the cost of care for patients with bone metastases. In a study of 534 patients with lung cancer and bone metastases, costs of treatment associated with SREs (including increased rates of hospitalization and rehabilitation) were \$9,480 per patient, and total medical care costs were \$27,982 greater for SRE patients than for patients without SREs.⁸ These figures do not include indirect costs associated with missed work by patients and family members.

Normal and Abnormal Bone Physiology

A comprehensive knowledge of normal bone physiology is essential to understanding the pathophysiology of bone metastases and the mechanisms of action of current treatments. An understanding of the process of bone remodeling is also important for identifying potential therapeutic targets.

What do we know about normal bone physiology and remodeling?

Normal bone remodeling, or bone turnover, is an ongoing process that results from the continuous resorption of mineralized matrix by osteoclasts

Improving the Management of Cancer-Related Bone Complications

(bone-resorption cells) coupled with the subsequent replacement of lost bone at numerous skeletal sites by osteoblasts (bone-forming cells).^{3,9} The balance between bone resorption by osteoclasts and bone formation by osteoblasts is maintained through a complex regulatory system of systemic and local factors. For example, hormonal factors (eg, estrogens and androgens) promote net bone formation by decreasing the formation, activation, and life span of osteoclasts and by increasing the formation, differentiation, proliferation, and activity of osteoblasts.¹⁰

The local cytokine microenvironment plays a critical role in the regulation of bone remodeling activity. Receptor activator of nuclear factor- κ B ligand (RANKL) is an essential cytokine that binds to the RANK receptor expressed on osteoclasts and promotes osteoclast formation and prolonged osteoclast life span. RANKL also promotes formation of the ruffled border in osteoclasts that allows them to attach to the bone surface and break down bone.^{3,9,11}

Osteoprotegerin (OPG) acts as a decoy receptor, blocking the action of RANKL and suppressing osteoclast formation. The balance between RANKL and OPG, in turn, is influenced by a host of other factors, including parathyroid hormone (PTH), parathyroid hormone-related protein (PTH-RP), 1,25-dihydroxyvitamin D₃, prostaglandin E₂, and interleukins.^{3,9}

How does malignancy affect bone physiology?

Any process that disrupts the normal homeostasis between bone formation and bone resorption will result in bone loss or destruction and increase

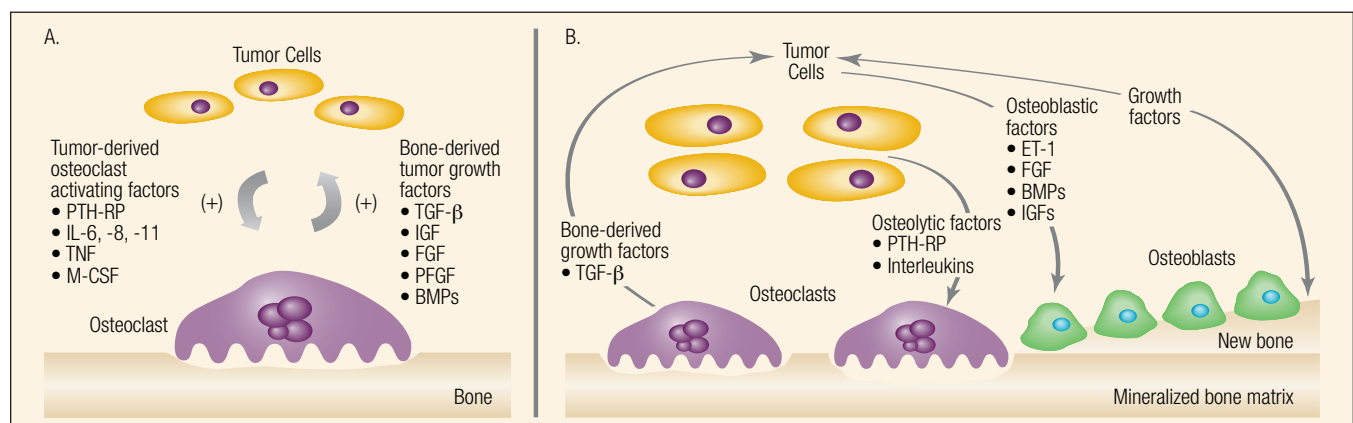
the risk of SREs. In the context of malignancy, this most often occurs via an interaction between the bone microenvironment and malignant cells, the result of which is the production of lesions that are either osteolytic (characterized by increased bone resorption with little bone formation) or osteoblastic (characterized by increased bone formation). The local bone microenvironment has thus emerged as a potential target for therapeutic agents directed at reducing tumor burden and improving outcomes.^{12,13}

Osteolytic bone metastases are most common in multiple myeloma as well as in lung, renal, and breast cancers. These lesions result from tumor-derived factors that activate osteoclasts via the RANKL pathway. These factors include interleukins (interleukins 6, 8, and 11), macrophage inflammatory protein-1 α , tumor necrosis factor, prostaglandin E₂, and PTH-RP. Subsequent bone resorption results in the release of growth factors that promote further tumor growth. This reciprocal relationship between tumor cells and osteoclasts establishes a vicious cycle of bone destruction and tumor growth, which increases the overall tumor burden (Figure 1).^{11,12} The presence of malignant cells within the bone marrow may serve as a reservoir of tumor cells and thereby increase the risk of metastasis to other distant sites.

Osteoblastic bone metastases involve a similar vicious cycle of interaction between the malignancy and bone. Osteoblastic bone metastases are most commonly seen in patients with prostate cancer. Tumor cells directly contribute to osteoblastic lesions primarily by producing endothelin-1 and other factors that stimulate osteoblast activity and the subsequent release of growth factors from bone that enhance tumor growth.^{3,9,13}

Figure 1. Pathogenesis of osteoclastic and osteoblastic metastases.¹² (A. Osteoclastic Metastases; B. Osteoblastic Metastases).

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Diagnosis of Bone Metastasis

Optimal management of bone metastasis requires a proactive approach to diagnostic and treatment strategies.

What diagnostic testing is indicated?

For patients who have high-risk cancers and symptoms of SREs, such as back pain and fractures, the decision to assess for bone metastases is

relatively straightforward. In the absence of symptoms, however, the benefit of diagnostic modalities is less clear. Over the past decade, guidelines for the diagnosis of bone metastases have been introduced for some, but not all, tumor types. The National Comprehensive Cancer Network (NCCN) recommends bone scans for the following categories of patients.^{14,15}

Breast cancer

1. Patients with stage I, II, or IIIa (T3N1M0) breast cancer with symptoms of localized SREs (eg, bone pain, neurologic deficits) or elevated alkaline phosphatase levels
2. Patients with stage IIIb, IIIc, or IV breast cancer

Prostate cancer

1. Symptomatic patients with prostate cancer and those with (a) life expectancy of >5 years, (b) T1 to T2 disease in the presence of a prostate-specific antigen (PSA) level >20 ng/mL, (c) Gleason score ≥ 8 , (d) T3 to T4 disease, or (e) symptomatic disease
2. Post-radical prostatectomy patients who develop an undetectable PSA level that becomes >0.3 ng/mL and rises on two or more determinations
3. Patients treated with radiotherapy who later develop a rising PSA level

Bone scans are *not* recommended for:^{15,16}

1. Patients with stage I or II breast cancer who are asymptomatic
2. Patients with multiple myeloma (bone scan underestimates the extent of pure osteolytic lesions)

Management of Bone Metastasis

The primary goal of therapy in patients with bone metastases is the prevention of SREs, rather than effecting an absolute change in bone mineral density. Several modalities can be employed, depending on the nature of the malignancy and the clinical indication. Options include radiation therapy (including radiopharmaceuticals) and procedural interventions (eg, vertebroplasty, kyphoplasty, and surgical stabilization).^{3,18} However, the main mode of treatment is the use of pharmacologic agents.

What is the pharmacologic treatment of choice?

Bisphosphonates are the primary pharmacologic agents used to treat bone metastases. These drugs inhibit bone resorption by inhibiting osteoclast activity and survival, thus reducing bone turnover, increasing bone mass, and improving mineralization.¹⁹

Several randomized, placebo-controlled trials have demonstrated that pamidronate (90 mg infused over 2 to 4 hours) significantly reduces the incidence of skeletal complications and delays their onset in patients with osteolytic lesions from multiple myeloma or metastatic breast cancer.²⁰⁻²² Other studies have reported that zoledronic acid (4 mg via 15-minute infusion) may be more potent than pamidronate. In the largest single trial of bisphosphonates (n=1,648), zoledronic acid was compared with pamidronate in patients with bone lesions from breast cancer or multiple myeloma.^{23,24} After 2 years, zoledronic acid reduced the overall risk of developing skeletal complications (including hypercalcemia of malignancy) by an additional 16% to 20% relative to pamidronate (Figure 2).^{23,24}

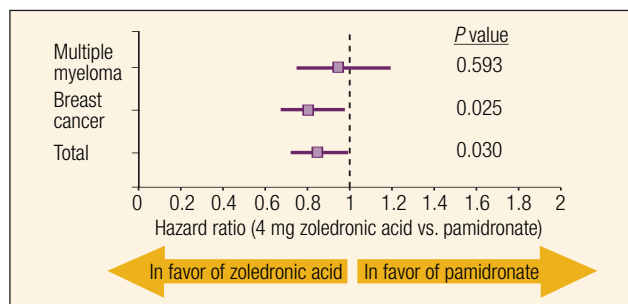
Zoledronic acid is the only bisphosphonate to demonstrate long-term efficacy in reducing SREs in men with advanced prostate cancer. In a 2-year study of zoledronic acid in men with metastatic hormone-refractory prostate cancer, zoledronic acid significantly reduced the percentage of patients with a skeletal complication by 36% compared with placebo.²⁵ It also reduced the percentage of patients who experienced each type of skeletal complication and reduced the mean skeletal morbidity (0.77 vs 1.47 SREs/year) compared with placebo.

Recent British guidelines¹⁶ recommend skeletal survey using plain radiography as the primary diagnostic test to detect bone lesions in patients with multiple myeloma. Subsequent characterization by diffusion magnetic resonance imaging or quantitative computerized tomography scan is indicated when imaging tests are ambiguous or providers wish to follow the progression or regression of bone disease over time. Other modalities, such as positron emission tomography scans and dual energy x-ray absorptiometry, are under investigation but are not currently recommended as screening tools for bone metastases.

Blood and urine levels of bone metabolic markers may be increased in patients with bone metastasis. While these markers are not yet considered to be reliable screening methods for metastasis to bone, some markers (eg, N-telopeptide, serum bone alkaline phosphatase) may be useful as prognostic indicators for skeletal complications in patients with known bone metastases.¹⁷ Further research is required to determine if these markers can help guide appropriate selection of patients for earlier institution of therapy.

Figure 2. Efficacy of zoledronic acid vs pamidronate.²⁴

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Zoledronic acid has also demonstrated efficacy in reducing SREs in other solid tumors, such as lung and renal cell cancer. In a 21-month study of lung cancer and other solid tumors (excluding breast and prostate), zoledronic acid significantly delayed the time to first SRE (236 days with zoledronic acid 4 mg vs 155 days with placebo).²⁶ The percentage of patients with at least one SRE was also reduced from 46% with placebo to 39% with zoledronic acid. In a separate analysis of patients with renal cell cancer, SREs occurred in 74% of patients given placebo but in only 37% treated with zoledronic acid.²⁷ The time to first SRE was 72 days in the placebo group but was not reached in the zoledronic acid group during the 9 months of study observation.

What are some of the controversies associated with bisphosphonate therapy?

Despite demonstration of the potency of bisphosphonates in reducing SREs in patients with bone metastases, there is still considerable uncertainty regarding the timing of therapy initiation, the duration of therapy, and dosing regimens. Furthermore, despite a large and growing body of evidence indicating a reduction in SREs with bisphosphonate treatments, evidence that bisphosphonates improve survival is only beginning to emerge.²¹⁻²³

Improving the Management of Cancer-Related Bone Complications

Consensus guidelines recommend initiating bisphosphonates at the time of diagnosis of bone metastasis and continuing their use for at least 2 years in all patients with multiple myeloma and in patients with breast cancer or prostate cancer who have radiologically confirmed bone metastases.^{28,29} Studies vary in terms of the dosing of bisphosphonates, but current guidelines for the treatment of multiple myeloma recommend intravenous pamidronate (90 mg infused over at least 2 hours) or zoledronic acid (4 mg infused over 15 minutes) every 3 to 4 weeks.²⁹

The optimal duration of therapy is unknown. Most studies use a treatment period of 2 years,^{5,21-23} but this is somewhat arbitrary. In the absence of any definitive data, one group suggests that treatment be given monthly for a period of 2 years.³⁰ If the patient's disease remains stable (ie, in a plateau phase) after the bisphosphonates have been discontinued, the patient can remain off treatment. If the patient still requires treatment, the frequency of infusions can be decreased to once every 3 months.³⁰ Patients who relapse after stopping bisphosphonates after 2 years, experiencing new onset of SREs, should resume treatment.^{29,30}

The use of intravenous bisphosphonate treatment can pose considerable challenges to a clinical oncology practice. Such therapy requires a commitment of office staff and time management. Reimbursement issues, concern for patient convenience, and the necessity of handling patients' fears regarding the risk of adverse events all add to the complexity of administering intravenous therapy in the office setting.

Despite these challenges, the recent evidence of survival benefits with bisphosphonates is encouraging. In a study of multiple solid tumors comparing the use of zoledronic acid and placebo, researchers found a significant reduction in the risk of death with zoledronic acid.³¹ Patients receiving zoledronic acid who had reduced amounts of bone turnover by serum markers had significant reductions in the risk of death, by 48% for patients with breast cancer, 59% for those with hormone-resistant prostate cancer, and 57% for those with lung cancer.³¹ Another study of lung cancer patients comparing zoledronic acid and placebo found a 35% reduction in the risk of death in patients receiving zoledronic acid.³²

What are some of the toxicities associated with bisphosphonate therapy?

Bisphosphonates are associated with several predictable toxicities (Table 2).³³ The most common is an acute-phase reaction upon initial infusion that manifests as bone pain, myalgia, nausea, fatigue, pyrexia, and emesis. This reaction occurs in a minority of patients. It is self-limiting, resolves

within 1 to 2 days, and can be treated with supportive care, including nonsteroidal anti-inflammatory drugs, acetaminophen, and adequate hydration. Reactions infrequently recur with subsequent infusion but are typically less severe.^{33,34}

Intravenous bisphosphonates can cause nephrotic syndrome and renal failure, particularly when administered in higher doses or over shorter infusion times. Guidelines from the American Society of Clinical Oncology (ASCO) recommend that creatinine be monitored prior to each dose of pamidronate or zoledronic acid. For patients with existing severe renal impairment (ie, serum creatinine >3.0 mg/dL or estimated creatinine clearance <30 mL/min) and extensive bone disease, pamidronate, administered over a protracted interval of 4 to 6 hours, is recommended. Zoledronic acid should not be used. Unexplained azotemia (an increase of ≥ 0.5 mg/dL in serum creatinine) should prompt temporary discontinuation of the bisphosphonate until renal function returns to 90% of baseline.^{28,29}

Most patients receiving high-potency bisphosphonates do not become hypocalcemic because of compensatory mechanisms, most importantly, increased secretion of PTH. However, in some cases, these compensatory mechanisms may be blocked (eg, prior parathyroidectomy, low vitamin D levels, hypomagnesemic hypoparathyroidism), resulting in hypocalcemia.³⁵ ASCO guidelines suggest periodic monitoring of serum magnesium, calcium, and phosphate during bisphosphonate therapy, although the time intervals for monitoring are not specified.²⁸

Osteonecrosis of the jaw (ONJ) is another risk of bisphosphonate therapy. ONJ tends to occur more frequently in patients with multiple myeloma and in older patients. It is also more commonly associated with use of zoledronic acid and with longer duration of bisphosphonate treatment. Dental extraction is a risk factor for the development of ONJ. Concomitant use of thalidomide and steroids with bisphosphonates also raises the risk for this complication.^{34,36,37} The frequency of bisphosphonate-induced ONJ is estimated at <1%, but it may be higher in patients with multiple myeloma (2% to 10%).^{38,39}

Prior to the initiation of therapy with an intravenous bisphosphonate, patients should be counseled about the possible occurrence of ONJ. They should be advised to identify and rectify dental problems prior to starting treatment and to avoid invasive dental procedures (tooth extraction and surgery to the jaw) during the course of therapy. Patients' oral hygiene status should be closely monitored during treatment with these agents.⁴⁰

Table 2. Potential toxicities associated with intravenous bisphosphonates.³³

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Adverse Event	Severity	Prevention	Response
Acute-phase reaction	Mild	Analgesics before dosing	Analgesics
Bone pain	Mild	Analgesics	Analgesics
Hypocalcemia	Mild to severe	Ensure adequate calcium and vitamin D intake; identify predisposing comorbidities (eg, high bone remodeling or hypoparathyroidism)	Provide calcium and vitamin D or stop treatment as appropriate
Local injection-site reactions	Mild	Good cannulation technique	Wound care
Nephrotoxicity	Severe	Assess renal function before and during treatment; ensure administration strictly follows manufacturer's protocol	Stop treatment
Osteonecrosis of the jaw	Severe	Assess and ensure oral health before treatment; monitor oral health during treatment	Consider stopping treatment; dental care

Once ONJ has occurred, conservative management with limited debridement, antibiotic therapy, and topical mouth rinses may result in healing, although some cases become chronic and cause further complications.⁴⁰ Surgical resection of necrotic bone may lead to disease progression and thus should be reserved for refractory cases.⁴⁰ There are

no prospective data to indicate whether bisphosphonate therapy should be discontinued once ONJ has been identified. This decision must weigh the detrimental clinical effects of the ONJ on the patient against the potential benefits of ongoing bisphosphonate therapy for preventing skeletal complications.⁴⁰

Summary

- Patients with breast cancer, prostate cancer, and multiple myeloma are at high risk of bone metastases.
- Skeletal-related events are common if patients with bone metastasis go untreated, and these complications result in considerable morbidity, mortality, and economic costs.
- An understanding of the dynamic state of bone remodeling can help identify therapeutic targets for the treatment or prevention of bone metastasis.
- Skeletal survey or computerized tomographic scan is the test of choice for diagnosing bone involvement in patients with multiple myeloma; bone scan is the preferred method in patients with other tumor types.
- Bisphosphonates reduce the incidence of skeletal-related events and increase survival in patients with bone metastasis.
- Toxicities associated with bisphosphonates include acute-phase reactions, renal failure, hypocalcemia, and osteonecrosis of the jaw.

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Improving the Management of Cancer-Related Bone Complications

Posttest Questions

Please select the best answer, and circle your response on the answer sheet provided on page 10.

1. The third most common site of solid tumor metastasis is the

- a. Liver
- b. Lung
- c. Brain
- d. Bone

2. Which cancer is associated with the highest incidence of skeletal-related events (SREs)?

- a. Breast
- b. Lung
- c. Prostate
- d. Renal

3. Nuclear factor- κ B ligand (RANKL) binds to the RANK receptor expressed on

- a. Osteoblasts
- b. Osteoclasts
- c. Bone matrix
- d. Tumor cells

4. Osteoprotegerin (OPG), when involved in bone remodeling,

- a. Attaches to the RANK receptor, suppressing osteoclast formation
- b. Acts as a decoy receptor, inducing the actions of RANKL
- c. Acts as a decoy receptor, blocking the actions of RANKL
- d. Influences parathyroid hormone (PTH), PTH-related protein (PTH-RP), and interleukins

5. Intravenous bisphosphonate therapy at higher doses or with shorter infusion times than recommended can result in

- a. Glomerulosclerosis
- b. Acute interstitial nephritis
- c. Nephrotic syndrome
- d. Liver toxicity
- e. Pancreatitis

6. The risk of osteonecrosis of the jaw (ONJ) is greatest with which of the following malignancies?

- a. Multiple myeloma
- b. Breast cancer
- c. Prostate cancer
- d. Lung cancer

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POSTTEST ANSWER SHEET

Circle only one answer per question.

- a b c d
- a b c d
- a b c d
- a b c d
- a b c d e
- a b c d

Evaluation Form

Improving the Management of Cancer-Related Bone Complications

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

If you felt the activity was biased, please explain:

2. Rate the extent to which this activity helped you to achieve the following objectives:	Strongly Agree					Strongly Disagree				
	5	4	3	2	1	5	4	3	2	1
• Explain the clinical impact of bone metastases with respect to skeletal-related events	5	4	3	2	1	5	4	3	2	1
• Describe the pathophysiology of bone metastasis	5	4	3	2	1	5	4	3	2	1
• Summarize the current standards for the treatment and prevention of skeletal-related events in patients with cancer that has metastasized to the bone	5	4	3	2	1	5	4	3	2	1
• Assess the risks and benefits associated with current therapies for bone metastasis	5	4	3	2	1	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
 Announcement postcard
 Colleague
 E-mail
 Other *(Please specify.)* _____

6. Time spent completing this activity?

- <.5 hr
 .5-.75 hr
 .75 hr
 >.75 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 activity
 Podcast
 Teleconference
 Journal supplement
 Newsletter/monograph
 Other *(Please specify.)* _____

Thank you for taking time to complete this evaluation.

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