New Currents in Treatment of Bone Metastases: A Case-Based Approach

Part 1 of 5: Overview of Bone Metastases and Bisphosphonates

Dear Colleague:

Skeletal complications of malignancy—bone pain, pathologic fractures, spinal cord compression, and hypercalcemia—greatly decrease quality of life and are associated with considerable morbidity and mortality. Bisphosphonates offer an effective way to help prevent skeletal-related events in patients with bone metastases from solid tumors. In this 5-part continuing education activity, New Currents in Treatment of Bone Metastases: A Case-Based Approach, leading medical oncologists discuss important data on bisphosphonates—including the newest research—and formulate specific patient-care guidelines illustrated in sample clinical cases.

This 5-part series opens with an overview of bone metastases and bisphosphonates (Part 1), and continues with four additional case-based discussions (Parts 2–5) of the use of bisphosphonates in treating skeletal complications of breast, prostate, renal, and lung cancers. This allows an in-depth look at specific patient populations and information on applying the data on bisphosphonates to actual clinical practice.

Each issue in this 5-part series consists of a Tx Reporter newsletter, an audio CD featuring an interview of the expert faculty on related issues, and a recent reprint with information that has largely determined the current standard of care. These issues focus on the next generation of bisphosphonate therapy. However, fair balance is critical to this discussion, and the faculty and I also present data on other bisphosphonates.

Here in Part 1 you will find a thorough overview explaining why specific management of bone metastases to prevent skeletal complications is so important. The discussion of bisphosphonates will provide you with an overview of the key data and clinical guidelines that will be explored more in depth in the case studies that follow in Parts 2 through 5. I hope that you enjoy the series and find it helpful and informative.

Yours truly,

Chair
James R. Berenson, MD
Chief Executive Officer
Institute of Cancer Therapies
Los Angeles, California

Part 1 of a 5-Part Series

This Tx Reporter series discusses the use of bisphosphonates to help prevent skeletal-related events in patients with bone metastases from solid tumors. This first issue provides an overview of bone metastases, and the use of bisphosphonates in cancer therapy and their important role in preventing skeletal complications.

This continuing professional education activity also includes the enclosed audio CD, in which faculty discuss:

• The devastating effects of bone metastases in their various clinical populations
• Effects of bone turnover on tumor growth
• Key clinical trials of bisphosphonates
• The potential antitumor activity of bisphosphonates
• Practical guidelines for using bisphosphonates

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Download this 5-part series—New Currents in Treatment of Bone Metastases: A Case-Based Approach—at www.projectsinknowledge.com/oncol/
Introduction

More than 400,000 US cancer patients are diagnosed annually with bone metastases; bone is the sole site of metastases in 28%. Incidence and prognosis vary according to primary cancer (Table 1).

<table>
<thead>
<tr>
<th>Bone Metastases</th>
<th>Median Survival (Years)</th>
<th>5-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma</td>
<td>96–97</td>
<td>10</td>
</tr>
<tr>
<td>Breast</td>
<td>65–75</td>
<td>24</td>
</tr>
<tr>
<td>Prostate</td>
<td>65–75</td>
<td>40</td>
</tr>
<tr>
<td>Lung</td>
<td>35–40</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Kidney</td>
<td>25–35</td>
<td>6–10</td>
</tr>
<tr>
<td>Thyroid</td>
<td>60</td>
<td>18–40</td>
</tr>
<tr>
<td>Melanoma</td>
<td>14–45</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Table 1. Incidence and Prognosis of Cancer Patients with Bone Metastases

Bone metastases can cause pain, pathologic fractures, nerve compression, immobility, and hematopoietic and spinal cord compromise. Extreme bone destruction or resorption can result in hypercalcemia, which produces significant symptoms and may be fatal. Therefore, preventing skeletal complications is critical.

Normal Bone Remodeling

The skeleton4:
- Supports tissues and levers for muscle
- Protects the central nervous system
- Houses bone marrow

To maintain these functions, bone is continuously broken down and remodeled. Approximately 10% of the skeleton is remodeled every year.Bone is continuously broken down and remodeled. Approximately 10% of the skeleton is remodeled every year.

Normal bone has an intricate system of bone remodeling, which is essential for bone health. This system involves the coordinated activity of osteoblasts and osteoclasts, which are responsible for bone formation and bone resorption, respectively.

Bone remodeling is a complex process that involves the continuous turnover of bone matrix. This process is regulated by various factors, including hormones, growth factors, and cytokines.

Bone remodeling is essential for bone health, as it allows for the replacement of damaged or worn-out bone with new, healthy bone. This process helps to maintain bone strength and structure, which is necessary for overall health and mobility.

Bisphosphonates

Bisphosphonates are a class of drugs that are used to treat bone metastases. They work by inhibiting osteoclastic bone resorption, which helps to reduce pain, improve mobility, and prevent fractures.

Bisphosphonates are administered intravenously or orally and are effective in reducing bone pain and improving quality of life for patients with bone metastases.

Mechanism

Bisphosphonates inhibit osteoclast activity by blocking the action of various signaling molecules, including cytokines and growth factors.

Bisphosphonates are also known for their ability to inhibit the proliferation and differentiation of osteoblasts, which helps to reduce bone formation and slow the progression of bone metastases.

Bone metastases can lead to significant complications, including pain, fractures, and loss of mobility. Bisphosphonates help to reduce these complications and improve overall quality of life for patients with bone metastases.

Bone metastases usually cannot be cured, and treatment with systemic chemotherapy, radiation, angiosomes, or orthopedic management is generally palliative. Bisphosphonates are the most effective agents available to inhibit bone resorption, and are the only agents approved to date for the treatment of bone metastases.

Bisphosphonates are generally well tolerated, with the most common side effects being nausea, vomiting, and constipation. However, patients should be monitored closely for signs of bone pain, fractures, or other complications.

Conclusion

Bisphosphonates are an important class of drugs for the treatment of bone metastases. They are effective in reducing pain, improving mobility, and slowing the progression of bone metastases. While bisphosphonates are not a cure for bone metastases, they are an important component of the treatment plan for patients with this condition.
overview of efficacy
Bisphosphonates include first-generation oral agents clodronate and etidronate, second-generation intravenous (IV) agent pamidronate, and third-generation IV agent zoledronic acid. Another third-generation bisphosphonate, ibandronate, is being investigated in both oral and IV formulations. Etidronate, risedronate, and alendronate are used to treat osteoporosis and other bone diseases but are not currently used for bone metastases. Oral bisphosphonates tend to be poorly absorbed and cause gastrointestinal irritation. In a Canadian study, daily oral etidronate (5 mg/kg) did not reduce skeletal complica-tions for patients with multiple myeloma who also received chemotherapy. In a randomized, placebo-controlled trial, clodronate approximately halved the proportions of multiple myeloma patients with severe hypercalcemia or nonvertebral fractures. It also reduced biochemical indices of bone turnover and the incidence of vertebral fractures. In long-term follow-up (median 8.6 years) clodronate may have prolonged survival. Similarly, in breast cancer, clodronate significantly reduced the incidence of vertebral fractures/deformities and hypercalcemia episodes, as well as the rate of metastatic skeletal-related events (SREs), and it prolonged the time to first SRE. However, in a comparative study, clodronate was less effective than pamidronate in controlling pain and suppressing bone resorption.

Oral pamidronate (300 mg/d) failed to reduce skeletal-related morbidity compared with placebo in a double-blind study of 300 patients with multiple myeloma. In contrast, IV pamidronate (90 mg as a 4-hour infusion for 21 cycles) reduced the proportion of multiple myeloma patients who developed any SRE (P = .015) and the mean number of SREs per year (1.3 versus 2.2 with placebo, P = .006), and improved survival in the subgroup who received concurrent second-line chemotherapy (14 versus 21 months; P = .041).

Pamidronate was also found superior to ibandronate in reducing osteoclast activity, bone resorption, IL-6, and possibly tumor burden in patients with multiple myeloma. In phase III placebo-controlled studies, pamidronate significantly reduced the proportion of metastatic breast cancer patients with skeletal complications (51% versus 64%) and skeletal morbidity rate (2.4 versus 3.7 events/y), and prolonged the time to first skeletal complication (12.7 versus 7 months). It also reduced pain scores and the need for analgesia. As a result, pamidronate became the standard of care for treatment of breast cancer bone metastases. Within the past year, pamidronate has been increasingly supplanted by zoledronic acid. In a phase III study of breast cancer and myeloma patients, the proportion of patients with at least one fracture and the median time to first SRE were similar with zoledronic acid or pamidronate. Zoledronic acid was associated with a slightly lower skeletal morbidity rate and event rate for radiation therapy to bone (Table 2). A recent Anderson-Gill multiple event analysis of this study, accounting for all clinically relevant SREs, showed a significantly lower SRE risk with zoledronic acid 4 mg (0.816) compared with pamidronate 90 mg (P = .042). Administration is also shorter: zoledronic acid is given as a 15-minute IV infusion, whereas pamidronate is a 2-hour IV infusion. Both agents have similar safety profiles and tolerability.

Zoledronic acid has also been studied in other cancers. A phase III study in patients with hormone-refractory prostate cancer and bone metastases found that zoledronic acid (4 mg Q3wk for 15 months) reduced the incidence of SREs, showed a significantly lower SRE risk with zoledronic acid 4 mg (0.816) compared with pamidronate 90 mg (P = .042). Administration is also shorter: zoledronic acid is given as a 15-minute IV infusion, whereas pamidronate is a 2-hour IV infusion. Both agents have similar safety profiles and tolerability. A double-blind, randomized, placebo-controlled trial of IV ibandronate in multiple myeloma showed no clinical benefit. However, a pooled analysis of two phase III trials in breast cancer patients with bone metastases found significant reductions with ibandronate (50 mg QD for 96 weeks) versus placebo in skeletal morbidity period rate (0.95 versus 1.18, P = .004) and number of bone events per patient (1.15 versus 1.85, P = .008).

Ibandronate reduced pain scores and analgesic use, and improved performance status and quality of life. In contrast to earlier oral bisphosphonate formulations, oral ibandronate 50 mg appears to have a lower incidence of gastrointestinal effects, similar to placebo. Ibandronate and other bisphosphonates have not been compared.

**Table 2. Zoledronic Acid Versus Pamidronate in Patients with Breast Cancer or Myeloma: Skeletal Morbidity Rate**

<table>
<thead>
<tr>
<th>SRE (−HCM) at month 13</th>
<th>44%</th>
<th>46%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All SREs (−HCM)</td>
<td>1.13 ± 3.98</td>
<td>1.40 ± 4.31</td>
</tr>
<tr>
<td>All SREs (+HCM)</td>
<td>1.13 ± 3.98</td>
<td>1.47 ± 4.40</td>
</tr>
<tr>
<td>Pathologic fracture</td>
<td>0.62 ± 1.03</td>
<td>0.86 ± 1.17</td>
</tr>
<tr>
<td>Vertebral fracture</td>
<td>0.27 ± 0.62</td>
<td>0.27 ± 0.70</td>
</tr>
<tr>
<td>Nonvertebral fracture</td>
<td>0.41 ± 0.85</td>
<td>0.45 ± 0.94</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>0.03 ± 0.22</td>
<td>0.09 ± 0.80</td>
</tr>
<tr>
<td>Radiation to bone</td>
<td>0.47 ± 3.83</td>
<td>0.71 ± 4.12</td>
</tr>
<tr>
<td>Surgery to bone</td>
<td>0.11 ± 0.28</td>
<td>0.10 ± 0.36</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>0.02 ± 0.15</td>
<td>0.06 ± 0.94</td>
</tr>
</tbody>
</table>

*Number of events per year (±); †P = .016; SRE = skeletal-related event; HCM = hypercalcemia of malignancy; SD = standard deviation. Adapted from Ruus et al. Cancer J 2001;7:377-387. Adapted with permission of Jones and Bartlett Publishers.*

**Clinical Guidelines**
All solid-tumor patients with evidence of lytic disease should be considered candidates for bisphosphonate therapy if they have an elevated creatinine level (>3 mg/dL for zoledronic acid or >5 mg/dL for pamidronate) or very extensive and symptomatic extraskeletal disease. To administer 4 mg IV zoledronic acid, add 5 mL sterile water for injection to the vial and dissolve the drug completely.
Further dilute the solution in 100 mL sterile 0.9% sodium chloride or 5% dextrose injection and infuse over no less than 15 minutes. Repeat every 3 to 4 weeks, and ensure adequate hydration prior to each dose. The optimal duration of treatment has not been determined, but there is some evidence supporting continued therapy even after a first SRE.25 Measure serum creatinine before each admission to monitor, and withhold treatment for renal deterioration (ie, an increase of ≥0.5 mg/dL if baseline was normal or ≥1.0 mg/dL if baseline was abnormal). Resume treatment at a slower infusion rate once creatinine level returns to baseline. If renal dysfunction continues, consider another bisphosphonate.

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Bone metastases are a common and serious problem associated with malignancy. Skeletal complications such as bone pain, fractures, nerve compression, immobility, hemopoietic and spinal cord compromise, and hypercalcemia greatly increase morbidity and mortality. Prevention of SREs is therefore an important component of management of bone metastases. All patients with bone metastases should be considered candidates for bisphosphonate therapy, particularly zoledronic acid for patients with creatinine levels ≤3 mg/dL. In clinical trials of patients with bone metastatic disease, zoledronic acid reduced SRE rates, pain and the need for analgesics, hypercalcemia, the need for palliative radiotherapy and orthopedic surgery, and the incidence of pathologic fractures. It is at least as safe and effective as pamidronate in breast cancer and myeloma, and is faster and more convenient to administer. It has also been found more effective than placebo in patients with bone metastases from a variety of other solid tumors, including prostate, lung, renal, and thyroid cancer. Zoledronic acid is the only bisphosphonate that has shown efficacy in these other solid tumors.35

Conclusions
Bone metastases are a common and serious problem associated with malignancy. Skeletal complications such as bone pain, fractures, nerve compression, immobility, hemopoietic and spinal cord compromise, and hypercalcemia greatly increase morbidity and mortality. Prevention of SREs is therefore an important component of management of bone metastases. All patients with bone metastases should be considered candidates for bisphosphonate therapy, particularly zoledronic acid for patients with creatinine levels ≤3 mg/dL. In clinical trials of patients with bone metastatic disease, zoledronic acid reduced SRE rates, pain and the need for analgesics, hypercalcemia, the need for palliative radiotherapy and orthopedic surgery, and the incidence of pathologic fractures. It is at least as safe and effective as pamidronate in breast cancer and myeloma, and is faster and more convenient to administer. It has also been found more effective than placebo in patients with bone metastases from a variety of other solid tumors, including prostate, lung, renal, and thyroid cancer. Zoledronic acid is the only bisphosphonate that has shown efficacy in these other solid tumors.
New Currents in the Treatment of Bone Metastases: A Case-Based Approach, Part 1

Instructions for Documentation of Participation in this activity:
To receive an acknowledgment of your participation for CME/CPE/CE credit, please complete the following steps:

1. Carefully read this newsletter and listen to the audio CD.
2. Complete the Posttest below, selecting the most appropriate response to each question.
3. Complete the Evaluation.
4. Send photocopies of the Posttest and Evaluation to Projects In Knowledge, Overlook at Great Notch, 150 Clove Road, Little Falls, NJ 07424, or fax to: 973-890-8822 by December 8, 2004.

If you complete these steps and score 70% or higher, Projects In Knowledge will mail you an acknowledgment of participation for up to 1 hour of CME credit for physicians, 1 contact hour of credit for pharmacists, or 1.2 contact hours for nurses within 6 weeks of receipt of your materials. If you score lower than 70%, Projects In Knowledge will notify you by mail and you will be given another chance to take the Posttest.

Name __________________________________________________________________ Degrees/Credentials _________________
Mailing Address _____________________________________________________________________________________________
City _____________________________________________________________________ State ________ ZIP ________________
Phone ________________________________________________ Fax _________________________________________________
E-mail _____________________________________________________________________________________________________

Please indicate your answers below.

1. Patients with which of the following metastases to bone have a median survival of >1 year?
   a. Breast
   b. Prostate
   c. Thyroid
   d. Myeloma
   e. All of the above

2. In normal bone homeostasis, osteoclastogenesis is triggered by:
   a. PTHrP
   b. RANK-L binding to the RANK receptor
   c. RANK-L binding to OPG
   d. TGFβ
   e. All of the above

3. Blastic lesions are associated with formation of bone that is:
   a. Solid and strong
   b. Weak and sclerotic
4. Which of the following has been clearly demonstrated to inhibit bone resorption in patients with bone metastases?
   a. Radiation therapy
   b. Systemic radiopharmaceuticals
   c. Chemotherapy
   d. Hormone therapy
   e. Bisphosphonates
   f. All of the above

5. Which of the following is false regarding the effects of bisphosphonates?
   a. They inhibit osteoclast activity and/or induce osteoclast apoptosis.
   b. Nitrogen-containing bisphosphonates inhibit tumor cell adhesion to bone.
   c. In vitro, when combined with chemotherapy, they appear to have synergistic apoptotic effects on breast cancer cells.
   d. They inhibit growth of primary soft-tissue lesions.

6. Which of the following has been proven to reduce skeletal complications in both osteolytic and osteoblastic lesions?
   a. Clodronate
   b. Pamidronate
   c. Zoledronic acid
   d. Ibandronate
   e. All of the above

7. Which of the following may increase the risk of renal toxicity with bisphosphonates?
   a. Multiple cycles
   b. Higher than recommended dose
   c. Shorter than recommended infusion time
   d. All of the above

8. In a study of myeloma and breast cancer patients with metastases to bone, compared with pamidronate, zoledronic acid was associated with:
   a. A significantly smaller proportion of patients with at least one SRE
   b. A significantly shorter median time to first SRE
   c. A significantly lower event rate for radiation to bone
   d. Less convenient administration due to longer administration time
   e. All of the above

9. Solid-tumor patients with evidence of lytic disease on imaging and creatinine levels ≤3 mg/dL should be considered candidates for bisphosphonate therapy with zoledronic acid.
   a. True
   b. False

10. Which bisphosphonate would be the most appropriate choice for a patient with bone metastases and a creatinine level of 4 mg/dL?
    a. Pamidronate
    b. Zoledronic acid
    c. No bisphosphonate should be used

Thank you for your participation.
New Currents in the Treatment of Bone Metastases: A Case-Based Approach, Part 1

CME/CE PARTICIPANT EVALUATION

Name _____________________________________________________ Degrees/Credentials ____________________________________________
Address ___________________________________________________________________________________________________
City ______________________________________________________ State ________________ ZIP _______________________

Instructions: Please complete this survey, along with the Posttest, and mail or fax (both sides) to Projects In Knowledge, Overlook at Great Notch, 150 Clove Road, Little Falls, NJ 07424; fax: 973-890-8822.

1. Please rate the extent to which you achieved the learning objectives:

- Review the incidence of bone metastases in patients with metastatic cancer, including multiple myeloma, breast, prostate, lung, kidney, thyroid, and other solid tumors.

- Describe the complications imposed by bone metastases in the clinical management of various solid tumors.

- Examine the mechanisms of action of bisphosphonates and their role in improving bone strength and inhibiting malignant cell function.

- Discuss the safety and efficacy of currently available agents and next generation bisphosphonates.

- Consider the use of intravenous therapy in the treatment armamentarium to delay and reduce skeletal complications of bone metastases in patients with multiple myeloma, breast, prostate, lung, kidney, thyroid, and other solid tumors.

- Describe appropriate techniques for administration of intravenous bisphosphonates.

- Improve quality of life for patients with bone metastases.

2. Please rate the relevance of the objectives to the overall purpose/goals of the educational activity:

- Review the incidence of bone metastases in patients with metastatic cancer, including multiple myeloma, breast, prostate, lung, kidney, thyroid, and other solid tumors.

- Describe the complications imposed by bone metastases in the clinical management of various solid tumors.

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- Improve quality of life for patients with bone metastases.
New Currents in the Treatment of Bone Metastases: A Case-Based Approach, Part 1

CME/CE PARTICIPANT EVALUATION

3. Please rate the overall value of this enduring material:
   [ ] Excellent [ ] Very Good [ ] Good [ ] Satisfactory [ ] Poor
   [ ] Strongly Agree [ ] Agree [ ] Disagree [ ] Strongly Disagree

4. Course was free from commercial bias:
   If you “Disagree” or “Strongly Disagree,” why?

5. Please rate the level of the material presented:
   [ ] Just Right [ ] Too Advanced [ ] Too Basic

6. Please list any changes in your practice that you would consider making as a result of participating in this activity:

7. Please rate your interest in self-directed or distance learning in the following formats:
   [ ] Very Interested [ ] Moderately Interested [ ] Not Interested
   a. Audioconference
   b. Videoconference
   c. Enduring materials (audiocassettes, videotapes, monographs)
   d. Internet (online discussions with experts, educational activities)
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8. Please tell us how long it took you to complete this course (in minutes):

9. Please list topics and/or experts you would find interesting and professionally relevant for future CME activities:

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Thank you for your participation.