ASCO SPECIAL ARTICLE

American Society of Clinical Oncology 2003 Update on the Role of Bisphosphonates and Bone Health Issues in Women With Breast Cancer

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Purpose: **To update the 2000 ASCO guidelines on the role of bisphosphonates in women with breast cancer and address the subject of bone health in these women.**

Results: **For patients with plain radiographic evidence of bone destruction, intravenous pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks is recommended. There is insufficient evidence supporting the efficacy of one bisphosphonate over the other. Starting bisphosphonates in women who demonstrate bone destruction through imaging but who have normal plain radiographs is considered reasonable treatment. Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction is not recommended. The presence or absence of bone pain should not be a factor in initiating bisphosphonates.**

In patients with a serum creatinine less than 3.0 mg/dL (265 μmol/L), no change in dosage, infusion time, or interval is required. Infusion times less than 2 hours with pamidronate or less than 15 minutes with zoledronic acid should be avoided. Creatinine should be monitored before each dose of either agent in accordance with US Food and Drug Administration (FDA) labeling.

Oncology professionals, especially medical oncologists, need to take an expanded role in the routine and regular assessment of the osteoporosis risk in women with breast cancer. The panel recommends an algorithm for patient management to maintain bone health.

Conclusion: **Bisphosphonates provide a supportive, albeit expensive and non–life-prolonging, benefit to many patients with bone metastases. Current research is focusing on bisphosphonates as adjuvant therapy. Although new data addressing when to stop therapy, alternative doses or schedules for administration, and how to best coordinate bisphosphonates with other palliative therapies are needed, they are not currently being investigated.**

J Clin Oncol 21:4042-4057. ***© 2003 by American Society of Clinical Oncology.***

THE AMERICAN Society of Clinical Oncology (ASCO) publishes evidence-based clinical practice guidelines. As part of the process, the expert panel reviews and updates the guidelines on a regular basis. This document represents an update of the guideline for the use of bisphosphonates in breast cancer that was published in 2000. The use of bisphosphonates in other solid tumors may be the subject of future ASCO clinical practice guidelines.

For the 2003 update, the Panel (see appendix) reviewed the published data since 2000. Computerized Medline searches were performed, meeting abstracts were reviewed, and members of the industry were contacted and given the opportunity to provide data. In preparing this update, it was decided that the related subject of bone health was important to consider. Although the initial impetus for this decision was the increasing utilization of nonsteroidal aromatase inhibitors, it is clear that the importance of bone health is not restricted to women receiving these agents. The ASCO Board of Directors approved this expansion in the scope of the guideline in November 2002.

The Panel had two meetings to consider the evidence for each of the 2000 recommendations. The guideline was circulated in draft form to the full expert panel and to the ASCO Health Services Committee for review and approval. The document was then reviewed and approved by the ASCO Board of Directors. Each recommendation from the 2000 guidelines is listed below, and is followed by an updated (2003) recommendation, if applicable. "No change" is indicated if a particular recommendation has not been revised. A summary of the evidence follows thereafter.

ASCO considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. It cannot be assumed that these guidelines apply to interventions performed in clinical trials, which are designed to test innovative and novel therapies in a disease for which better therapy is sorely needed. In that guideline development involves a review and synthesis of the latest literature, and a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.

Background

Since the publication of the 2000 guidelines on bisphosphonates in breast cancer, a variety of events have occurred that

From the American Society of Clinical Oncology, Alexandria, Virginia.

Submitted August 5, 2003; accepted August 12, 2003.

Adopted on May 30, 2003 by the American Society of Clinical Oncology.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/03/2121-4042/$20.00

DOI: 10.1200/JCO.2003.08.017

prompted this current update. Among these events is the approval of a new intravenous bisphosphonate, zoledronic acid, for use in women with breast cancer. Although discussed in the 2000 guidelines, clodronate continues to be available in the United States only as an investigational therapy. A new drug application to the US Food and Drug Administration (FDA) for clodronate has, to date, never been submitted. The potential renal toxicity of intravenous pamidronate and zoledronic acid has prompted specific recommended monitoring schedules by the FDA. The interest in assessing bisphosphonates as adjuvant therapy has expanded. Since 2000, two randomized clinical trials using oral clodronate as an adjuvant therapy have been reported. These issues will be subsequently discussed.

Although the Panel reviewed numerous publications on the subject since 2000, the vast majority of reports were reviews revisiting the small current collection of clinical trials. Since 2000, no major randomized controlled trials in the metastatic setting have been initiated. Therefore, it is unlikely that in the foreseeable future there will be any new data addressing the issues of when to start, stop, alternative dose, or schedule bisphosphonates. While some have criticized the original guidelines for recommending 'the extensive and early use of bisphosphonates',[1] there have been no efforts to systematically address the outstanding questions. The interest of the major clinical trial groups in the US, Canada, and Europe has shifted to the adjuvant setting. Several different trials have been, or are expected to be, initiated.

GUIDELINES FOR THE USE OF BISPHOSPHONATES IN BREAST CANCER

In these guidelines, recommendations about the indications for using bisphosphonates for bone disease in breast cancer are presented in the context of three clinical presentation scenarios for patients with breast cancer. These include women with imaging evidence of bone metastases, women with extra-skeletal metastases without evidence of bone metastases, and bisphosphonates as adjuvant therapy.

BISPHOSPHONATE USE IN WOMEN WITH IMAGING EVIDENCE OF BONE METASTASES

Lytic Disease on Plain Radiographs

2000 recommendation. Intravenous pamidronate 90 mg delivered over 1 to 2 hours every 3 to 4 weeks is recommended in women with metastatic breast cancer who have plain radiograph(s) that show lytic destruction of bone and who are receiving systemic therapy with hormonal therapy or chemotherapy.

2003 recommendation. For breast cancer patients who have evidence of bone destruction on plain radiographs, intravenous pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks are recommended. There is insufficient evidence supporting the efficacy of one bisphosphonate over the other. For each of the guidelines, clinical judgment should also take into consideration the patient's general performance status and overall prognosis.

Evidence Summary

The Panel based its revised recommendation on reviewing all of the available literature but specifically focused its critical appraisal on the single randomized comparison of zoledronic acid to pamidronate. A detailed comparison of the entry criteria, design, statistical planning and reporting, and results is listed in the 2002 ASCO multiple myeloma guidelines.[2] In addition, the guidelines were modified to indicate that the duration of infusion of pamidronate should be 2 hours rather than a shorter duration. The basis for this decision is related to the potential for renal toxicity as discussed in the section on safety and adverse events.

Pamidronate. There are no new randomized placebo controlled trials evaluating the use of intravenous pamidronate. Pamidronate was used as the control in the randomized comparison to zoledronic acid (discussed below). There are no new data addressing the optimal dose, duration, or dosing interval. There is new information on safety issues, specifically renal toxicities, discussed later.

Clodronate. There are no new reports of clodronate in the metastatic disease setting.

Zoledronic acid. In February 2002, the FDA approved an expanded indication for zoledronic acid that included its use in metastatic breast cancer and multiple myeloma (www.fda.gov/cder/cancer). This new indication is based on a large randomized comparison to pamidronate.

Two randomized trials showed that zoledronic acid can be given safely over a short interval and produce similar antiresorptive effects as administering 90 mg of pamidronate, as assessed by bone resorption markers. The first randomized phase II study, compared this newer bisphosphonate to pamidronate in 280 patients with lytic bone metastases from either myeloma (n = 108) or breast cancer (n = 172).[3] Patients were randomly assigned to nine monthly infusions of 0.4 mg, 2.0 mg, or 4.0 mg zoledronic acid in a 5-minute infusion, or to 90 mg pamidronate as a 2-hour infusion. The primary end point was to determine a dose(s) of zoledronic acid that reduced the need for radiation to less than 30% of treated women, although all skeletal related events (SREs) were also evaluated as in the previously reported pamidronate trials. SREs were an aggregate of all sites and number of pathologic fractures, spinal cord collapse/compression, and need for therapeutic radiation therapy, including pain and impending fracture. Duration of follow-up was not reported. Radiation treatment was required in a similar proportion of patients (18% to 21%) receiving pamidronate and zoledronic acid at 2.0 mg or 4.0 mg, whereas more patients (24%) receiving 0.4 mg zoledronic acid underwent radiotherapy. Similarly, the proportion of patients (30% to 35%) with any SRE was lower in the 2.0 mg and 4.0 mg zoledronic acid and the pamidronate groups compared with the 0.4 mg zoledronic acid group (46%). This phase II trial was not powered to show superiority of zoledronic acid compared to pamidronate.

In light of the above dose information, a larger phase III randomized trial compared 4 or 8 mg doses of zoledronic acid to 90 mg pamidronate every 3 to 4 weeks in multiple myeloma or breast cancer patients with lytic disease.[4] Due to rises in

creatinine that occurred more frequently among patients receiving zoledronic acid, the infusion time for zoledronic acid was increased from 5 minutes to 15 minutes during the trial. Despite this change, renal problems occurred more often among patients randomly assigned to 8 mg zoledronic acid, and as a result, the dose was reduced to 4 mg.

The trial's sample size was based on showing equivalence (noninferiority), not superiority, of zoledronic acid to pamidronate. Noninferiority was concluded if the observed difference was less than the upper limit of difference in the one-sided 95% CI in SRES between zoledronic acid and pamidronate—a difference of 8%. The trial's sample size was sufficient to have an 80% power using a one-sided significance of 0.05. The trial included 1,130 patients with metastatic breast cancer who were evaluated in the intent to treat analysis approximately every 3 months for 13 months.

Secondary end points of pain and performance status showed similar effects to those in prior studies. Details related to pain were not reported other than to say that 53% of patients had a pain score greater than zero at the beginning of the study and 69% had a decrease in their pain scores. The average decline in pain score was about 0.5 on a five-point scale. Analgesic use and Eastern Cooperative Oncology Group (ECOG) performance status over the 13 months were 'fairly stable'.

In all treatment groups, about 50% of patients reported an adverse event; however, less than 5% of those events were classified as drug-related. Seven percent of patients discontinued therapy because of an adverse effect. The frequency of serious renal-related adverse events was 1.9% in the higher dose (8 mg) zoledronic acid group compared with 0.5% in the 4 mg zoledronic acid group and 0.2% in the pamidronate group. After modifying the infusion schedule of zoledronic acid, it appears that the incidence of renal impairment declined, but the number of patients was small.

Novartis (East Hanover, NJ) provided additional follow-up data for the panel regarding the breast cancer patients in this trial. At 25 months, there was no difference in the proportion of patients having a SRE (46% to 48% with zoledronic acid *v* 49% with pamidronate). The median survival rate was also no different at ~25 months.

Subset analyses that were not preplanned found that patients initially treated with hormonal therapy and zoledronic acid compared with pamidronate needed less radiation therapy to the bone (0.33 events/yr *v* 0.58 events/yr; $P = .015$). This needs to be prospectively confirmed before its importance in guiding decision-making can be assessed.

Cook and Major[5] have recently highlighted that bone complications, especially fractures, may not be independent events but rather ones that occur in clusters. One advocated method to the statistical evaluation of these type of data is a multiple-event analysis.[6] This type of multiple event analysis using the Andersen-Gill methodology found zoledronic acid to be more effective than pamidronate.[7] This result, reported in abstract form only, is based on the total number of events and the time between events. Specifically, an 18% risk reduction for developing an SRE with 4 mg zoledronic acid was reported (hazard ratio [HR],0.82; 95% CI, 0.67 to 0.99; $P = .04$).[7]

Analyses based on multiple event data must be interpreted with care, especially in contrast to results using more straightforward analyses. Each of the commonly used statistical methods for multiple event analyses require more assumptions about the nature of the data and also require making somewhat arbitrary decisions about how to represent events in the analysis. The results from analyses using multiple event models need to be subjected to careful demonstrations of the stability of the conclusions when assumptions are varied.

Other guidelines. Several other groups or individuals have addressed the role of bisphosphonates in breast cancer. The Cochrane Breast Cancer Review Group has recently completed an extensive literature review of previously reported randomized trials evaluating bisphosphonates.[8] This review identified 19 randomized trials. In their analysis of eight studies involving 1,962 women with advanced breast cancer and existing bone metastases, bisphosphonates reduced the risk of developing a skeletal event by 14% (95% CI; risk ratio [RR], 0.80 to 0.91). For intravenous pamidronate, the reduction in the risk of skeletal event using a 90 mg dosage was 23% (95% CI; RR, 0.73 to 0.94) and for oral clodronate was 16% (95% CI; RR, 0.72 to 0.98; $P = .03$). Compared with placebo, bisphosphonates reduced the skeletal event rate by a median of 30% overall (range, 20% to 48%). They concluded, based on the single study discussed above, that zoledronic acid appeared to have equivalent efficacy when compared with intravenous pamidronate.

Another recent review addressed the role of oral bisphosphonates in myeloma and breast cancer and concluded that oral bisphosphonates do not appear to be as effective as those administered intravenously.[9]

In December 2002, Cancer Care Ontario updated its guidelines on the use of bisphosphonates in women with breast cancer (www.cancercare.on.ca/ccopgi).[8] Their guidelines recommend that women with breast cancer who have bone metastases should be offered treatment with oral clodronate or intravenous pamidronate. Intravenous zoledronic acid was considered an alternative to pamidronate when a shorter infusion time (15 minutes) is "important". No examples were given to guide providers in determining "importance". The remainder of the Cancer Care Ontario guidelines on the role of bisphosphonates in the adjuvant setting, pain control, and the absence of data on the optimal duration of therapy, agree with what is later discussed in this update.

Panel deliberations. Although the conclusions of the Cochrane Breast Cancer Group review suggest that both clodronate and pamidronate are likely to be superior to placebo, the judgment of the Panel was that the recommendation be made only for the use of intravenous pamidronate and zoledronic acid. Reasons for this recommendation include: (1) clodronate has not yet been approved for use in the U.S.; (2) the evidence for clodronate was clouded by the potential for an overestimation of its effect, based on the use of events per person per year; and (3) the inability to aggregate all the relevant skeletal end points. A review of the zoledronic acid/pamidronate protocol by the Panel confirmed that this multiple event assessment was one of at least seven preplanned secondary efficacy analyses of the comparative

trial. Multiple event analyses are statistically more complex, may be subject to after-the-fact assumptions, and ideally, should be independently validated. The Panel concluded that there was insufficient evidence to conclude that the effectiveness of zoledronic acid was superior to pamidronate. The publication of the full multiple event analysis report of this trial is awaited with interest.

Abnormal Bone Scan, Normal Radiographs but Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) Scan Showing Bone Destruction

2000 recommendation. Starting bisphosphonates in women with an abnormal bone scan and an abnormal CT or MRI scan showing bone destruction and localized pain, but normal plain radiographs, is considered reasonable by Panel consensus based on the findings in women with osteolytic changes on plain radiographs.

2003 recommendation. Starting bisphosphonates in women with an abnormal bone scan and an abnormal CT or MRI scan showing bone destruction, but normal plain radiographs, is considered reasonable by Panel consensus based on the findings in women with lytic or mixed lytic/blastic changes on plain radiographs.

Abnormal Bone Scan, Normal Radiographs, and No Evidence of Bone Destruction on CT or MRI

2000 recommendation. Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction on radiographs, tomograms, CT scans, or MRI, or with localized pain, is not suggested.

2003 recommendation. Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction on radiographs, CT scans, or MRI is not recommended.

SAFETY AND ADVERSE EFFECTS

2003 Recommendation. In patients with pre-existing renal disease and a serum creatinine level less than 3.0 mg/dL (265 μmol/L), no change in dosage, infusion time, or interval of pamidronate or zoledronic acid is required. Use of these bisphosphonates among patients with worse function has been minimally assessed. Infusion times less than 2 hours with pamidronate or less than 15 minutes with zoledronic acid should be avoided. The Panel recommends that serum creatinine should be monitored prior to each dose of pamidronate or zoledronic acid, in accordance with FDA-approved labeling. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly, even though there is no evidence on which to base a recommendation for time intervals. In contrast to multiple myeloma patients, there currently is no data to support routine assessments for albuminuria in breast cancer patients.

Evidence Summary

Short-term use of bisphosphonates, when administered according to recommended infusion doses, infusion times, and dosing intervals, is associated with a low risk of renal dysfunction. In a randomized comparison of pamidronate (90 mg as a 2-hour infusion) versus zoledronic acid (4 mg as a 15-minute infusion),[4] 6% to 8% of patients with breast cancer experienced deterioration of renal function during the first 12 months of bisphosphonate therapy. In that study, deterioration of renal function was defined as change in baseline serum creatinine $\geq$ 0.5 mg/dL or $\geq$ 2 times baseline value in patients with normal baseline serum creatinine ($<$1.4 mg/dL), or a change from baseline serum creatinine $\geq$ 1.0 mg/dL or $\geq$ 2 times baseline value in patients with abnormal baseline serum creatinine ($\geq$1.4 mg/dL). One of 365 patients in that trial developed grade 3 renal toxicity, according to the National Cancer Institute Common Toxicity Criteria (Personal communication, Hei YJ, Seaman J, Novartis Pharmaceuticals, 2003).

There are limited data on the long-term renal safety of bisphosphonates. In an uncontrolled study of 22 patients treated with pamidronate (n = 18) or zoledronic acid (n = 4) for more than 2 years (median, 3.6 years), the last serum creatinine level was significantly higher than baseline values.[10]

Although shorter infusion times may be tolerated on a short-term basis, shorter infusion times have been associated with a higher risk of renal toxicity. Intravenous infusions of pamidronate over less than 2 hours, especially those $\leq$ 1 hour given on a long-term basis ($>$ 1 year), have been occasionally associated with renal toxicity including albuminuria followed by azotemia. More serious renal toxicity has also been reported with long-term use of higher doses or more frequent dosing of pamidronate.[11-13] Most cases occurred among patients with multiple myeloma, although some also occurred among patients with breast cancer. The kidney pathology may show a collapsing focal segmental glomerulosclerosis[12,13] or tubulointerstitial nephritis.[11]

Recently, several case reports have been reported relating to adverse renal consequences with prolonged pamidronate use.[12,13] It is important to note that the appearance of renal dysfunction in these patients should lead the treating physician to hold the dose of pamidronate or zoledronic acid until there is resolution of the renal dysfunction. Based on the algorithm used in the comparative pamidronate versus zoledronic acid trials, if detected early, this renal dysfunction has been reversible in most cases. Retreatment of these patients with pamidronate or zoledronic acid has been tolerated without the return of kidney problems. Therefore, the development of renal dysfunction is cause for concern and warrants discontinuation of the drug until reversal of the renal abnormalities occurs. If the renal function does not return to normal, there are no data on which to base management. A prudent approach would be request consultation from a nephrologist and either indefinitely withhold bisphosphonate therapy or restart with close monitoring and a prolonged infusion time.

The Panel's specific recommendation was that the presence of unexplained renal dysfunction should warrant discontinuation of pamidronate or zoledronic acid until these renal problems have resolved. Unexplained renal dysfunction is defined as an increase of $\geq$ 0.5 mg/dL in serum creatinine or an absolute value of more than 1.4 mg/dL among patients with normal baseline serum creatinine levels. These patients should be reassessed every 3 to

4 weeks and pamidronate or zoledronic acid should be reinstituted cautiously when the renal function returns to baseline.

It is essential that physicians infuse pamidronate 90 mg at a rate no faster than 2 hours or zoledronic acid at a rate no faster than 15 minutes every 3 to 4 weeks and not attempt to shorten the infusion time, increase the dose, or reduce the dose interval.

The safety and frequency of nonrenal adverse events with zoledronic acid appear to be similar to pamidronate. The latter were well characterized in the pamidronate versus placebo trials[14,15] and the recent pamidronate versus zoledronic acid studies.[3,4] The incidence of most adverse effects in patients treated with pamidronate was similar to that observed in the placebo group. Transient myalgias, arthralgias, and flu-like symptoms with fever tend to occur more often in patients treated with pamidronate than placebo.[15,16] These symptoms usually occur only after the first and/or second infusion of pamidronate and are not an indication to discontinue treatment of the drug. Ocular side effects from pamidronate are a relatively rare but well-recognized complication, first reported in 1994.[17] An update review of case reports found 17 cases of unilateral scleritis and one case of bilateral scleritis, usually within 6 hours to 2 days after intravenous pamidronate. Six patients had positive rechallenge testing with the scleritis occurring again after a repeat drug exposure.[18]

The Panel recommends that serum creatinine should be monitored prior to each dose of pamidronate or zoledronic acid. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly.

The Panel deliberations focused on the lack of an operational definition of how regular is 'regular' blood chemistry assessment and the need to monitor serum creatinine prior to each dose of pamidronate or zoledronic acid. The FDA-approved labeling provides no guidance on time intervals for blood chemistry assessment, but is specific on pretreatment creatinine measurement. The Panel's recommendation is consistent with the current FDA-approved guidelines in the pamidronate and zoledronic acid package inserts. Those guidelines were not part of the initial pamidronate package insert, but were changed in a recent revision. The Panel recognizes that it may be difficult or inconvenient for some clinics to obtain results of renal function tests before pamidronate or zoledronic acid administration. However, the Panel recommends that the FDA-approved monitoring guidelines be followed.

Biochemical Markers

2000 recommendation. The use of the biochemical markers to monitor bisphosphonate use is not suggested for routine care.

2003 recommendation. No change.

Evidence Summary

Biochemical markers of bone resorption reflect the metabolic breakdown of type I collagen. Immunoassays have been developed to measure the N-terminal and C-terminal peptides of this collagen metabolism in urine and serum.[19] Currently, only radiographic evidence of bone metastases is a reliable stratifier of future risk of bone complications. Biochemical markers could assist clinicians as either prognostic factors or predictive factors of treatment response to bisphosphonates.

Available preliminary studies show that bone marker levels, especially urinary N-telopeptide (NTX), correlate with the extent of bone involvement and bone progression.[20] NTX was also found to be associated with future skeletal-related events, bone progression, and death in a recent report.[21] In a retrospective study using data collected during the pamidronate-zoledronic acid comparative trial,[4] baseline and serial bone markers were obtained from most patients. An elevated urinary NTX level at any time was associated in the subsequent 3 months with an increased risk of SRE, bone progression, or death. The relative risks reported for patients with an NTX greater than 100 nmol/mmol creatinine was 3.6 for a SRE, 3.2 for bone progression (not defined), and 6.7 for death, respectively.

However, the value of bone resorption markers to guide treatment decisions has not yet been shown, for example, to guide initiation of therapy in patients without a prior skeletal event, predict treatment response, guide adjustments to bisphosphonate therapy, or to independently predict future fractures. Each is a worthy goal, but can only be addressed in the research setting.

Duration of Therapy

2000 recommendation. The panel suggests that once initiated, intravenous bisphosphonates be continued until evidence of substantial decline in a patient's general performance status. The Panel stresses that clinical judgment must guide what is a substantial decline. There is no evidence addressing the consequences of stopping bisphosphonates after one or more adverse skeletal events.

2003 recommendation. No change.

Evidence Summary

The 2002 Cancer Care Ontario guidelines interpretative summary notes "that it is not known whether it is beneficial to continue bisphosphonates in patients who continue to experience skeletal events. In view of the costs of prolonged bisphosphonate therapy, this topic would be an appropriate area for future research."[22]

Role in Control of Pain Secondary to Bone Metastases

2000 recommendation. The Panel recommends that current standards of care for cancer pain, analgesics, and local radiation therapy should not be displaced by bisphosphonates. Intravenous pamidronate is recommended in women with pain as a result of osteolytic metastasis to relieve pain when used concurrently with systemic chemotherapy and/or hormonal therapy, because it was associated with a modest pain control benefit in controlled trials.

2003 recommendation. The Panel recommends that the current standards of care for cancer pain management must be applied throughout bisphosphonate therapy and is required by good clinical practice. These standards of care for pain management include analgesics, corticosteroids, interventional procedures, nonsteroidal anti-inflammatory agents, systemic radiopharmaceuticals, and local radiation therapy. Among other therapeutic options, intravenous pamidronate or zoledronic acid may be of benefit among women with pain caused by bone metastases to relieve pain when used concurrently with systemic

chemotherapy and/or hormonal therapy, because it was associated with a modest pain control benefit in controlled trials.

2000 recommendation. There is insufficient evidence to support a role for intravenous bisphosphonates as an adjunctive therapy to radiation therapy in women with pain as a result of metastatic bone disease when systemic chemotherapy and/or hormonal therapy is not being employed. The role of bisphosphonates vis-à-vis radiation therapy as the sole therapy in this setting has not been determined. In women already treated with local radiotherapy who have persistent or recurrent pain, bisphosphonates are an attractive but little studied salvage therapy.

2003 recommendation. No change.

Evidence Summary

A distinction should be made between the ability of bisphosphonates to relieve pain in patients with bone metastases from its ability to prevent pain from bone metastases.

A prospective case series by Groff[23] evaluated 200 patients with breast cancer or multiple myeloma who received 60 mg pamidronate in six infusions over 7 weeks, followed by one infusion every 3 weeks, for a total of 24 infusions concurrent with chemotherapy or radiation. Only 94 patients completed six infusions and only 25 patients completed all 24 infusions. The median equivalent daily dose of morphine ranged from 21 to 41 mg/d and either decreased or remained stable during the study. Given the lack of a control arm and concurrent therapy, the relative efficacy is difficult to interpret.

In the zoledronic acid versus pamidronate randomized, controlled clinical trial (discussed in detail in part I) the analgesic use stabilized or decreased in both groups, the median time to first SRE was approximately 12 months in all treatment groups, and the use of radiation therapy was decreased only among breast cancer patients treated with hormonal therapy.[4]

For women with pain as a result of bone metastases, no studies have compared the efficacy of intravenous bisphosphonates to that of radiotherapy. Like the approach used in curative therapies of combining chemotherapy and radiation, studies are needed that evaluate the combination of radiation (external beam radiation and/or radiopharmaceuticals) with chemotherapy, hormonal therapy, and bisphosphonates. Part of the difficulty in determining the best multidisciplinary approach also relates to the various types of clinical problems that require palliative care. Issues that specifically need to be addressed are how therapies can be combined to create additive or synergistic effects to achieve the most rapid palliation of symptoms, fewest treatment-related toxicities, and least amount of time under treatment, especially in a patient with a limited prognosis. The optimal complementary role of bisphosphonates needs to be further defined.

The Role of Bisphosphonates With No Radiographic Evidence of Bone Metastases

Extraskeletal Metastases Without Evidence of Bone Metastases

2000 recommendation. Starting bisphosphonates in women without evidence of bone metastases even in the presence of other extra-skeletal metastases is not recommended.

This clinical situation has not been studied using intravenous bisphosphonates and should be the focus of new clinical trials.

2003 recommendation. No change.

Bisphosphonates As Adjuvant Therapy

2000 recommendation. Inconsistent, evolving data have been found in studies with bisphosphonate use in the adjuvant setting to prevent osseous metastases. Starting bisphosphonates in women at any stage of their nonosseous disease, outside of clinical trials, despite a high risk for future bone metastasis, is currently not recommended.

2003 recommendation. No change.

BISPHOSPHONATES AS ADJUVANT TREATMENT FOR BREAST CANCER

Since the 2000 guidelines were published, the three randomized controlled trials of adjuvant clodronate in early stage breast cancer have been updated.[24-26] These three prospective randomized trials provide conflicting data on the potential role of adjuvant bisphosphonates among patients with no evidence of distant metastases after definitive local surgery. The findings from these studies were available in "first report" format at the time of publication of the 2000 guidelines, and each has since been updated. Table 2 provides a systematic tabular comparison of the trials.

The first trial conducted by Diel et al[26,27] randomly assigned 302 women with T1 to T4 and N0 to N2 primary breast cancer and immunocytochemical evidence of cancer (positive for tumor-associated glycoprotein-12) in a bone marrow aspirate to receive either clodronate 1,600 mg/d for 2 years or no bisphosphonate. The type of adjuvant systemic therapy was selected in accordance with specific guidelines. In the initial report, with a median follow-up of 36 months, the incidence of overall metastasis (13% *v* 29%), bone metastasis (8% *v* 17%), and visceral metastasis (8% *v* 19%) was more than cut in half (each $P < .003$). Particularly striking was the unanticipated finding that the clodronate group showed superiority in terms of metastasis-free survival and overall survival (96% *v* 85%; $P = .001$). The investigators provided an update of their initial report at the May 2000 ASCO meeting (New Orleans, LA). With an additional 2 years of follow-up, the extra-skeletal effect was no longer significant. However, the end points of reduction of bone metastases and improvement in disease-free survival (DFS) and overall survival (OS) remained statistically significant. At 5 years of follow-up, bone metastases were reduced in the clodronate group compared with a control group (14% *v* 24%; $P = .044$) and visceral metastases showed a trend toward reduction (17% *v* 26%; $P = .091$). Overall survival was higher in the clodronate arm (91% *v* 77%; $P = .002$). The effect of adjuvant clodronate appeared weakened with longer follow-up.

Powles et al[25] reported definitive results of their phase III trial presented in abstract form at the time of the 2000 guidelines. In this double-blind trial, 1,069 women were randomly assigned to receive either clodronate 1,600 mg/d or placebo starting 6 months after surgery, for a duration of 2

Table 1. Summary of Guidelines

Specific Guideline	2000 Recommendation	2003 Recommendation
Bisphosphonate use in women with imaging evidence of bone metastases		
Lytic disease on plain radiographs	Intravenous pamidronate at 90 mg delivered over 1 to 2 hours every 3 to 4 weeks is recommended in women with metastatic breast cancer who show lytic destruction of bone on plain radiograph(s), and who are receiving systemic therapy with hormonal therapy or chemotherapy	For breast cancer patients who have evidence of bone destruction on plain radiographs, intravenous pamidronate 90 mg delivered over 2 hours or zoledronic acid 4 mg over 15 minutes every 3 to 4 weeks are recommended. There is insufficient evidence relating to efficacy to support one bisphosphonate over the other. For each of the guidelines, clinical judgment should also take into consideration the patient's general performance status and overall prognosis
Abnormal bone scan, normal radiographs but CT or MRI scan showing bone destruction	Starting bisphosphonates in women with an abnormal bone scan and an abnormal CT or MRI scan showing bone destruction and localized pain, but normal plain radiographs, is considered reasonable by panel consensus based on the findings in women with osteolytic changes on plain radiographs	Starting bisphosphonates in women with an abnormal bone scan and an abnormal CT or MRI scan showing bone destruction, but normal plain radiographs, is considered reasonable by panel consensus based on the findings in women with lytic or mixed lytic/blastic changes on plain radiographs.
Abnormal bone scan, normal radiographs and no evidence of bone destruction on CT or MRI	Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction on radiographs, tomograms, CT scans, or MRI, or with localized pain, is not suggested	Starting bisphosphonates in women with only an abnormal bone scan but without evidence of bone destruction on radiographs, CT scans, or MRI is not recommended.
Safety and adverse effects		
Safety and adverse effects		In patients with pre-existing renal disease and a serum creatinine less than 3.0 mg/dL (265 μmol/L), no change in dosage, infusion time, or interval of pamidronate or zoledronic acid is required. Use of these bisphosphonates among patients with worse function has been minimally assessed. Infusion times less than 2 hours with pamidronate or less than 15 minutes with zoledronic acid should be avoided. The Panel recommends that serum creatinine should be monitored prior to each dose of pamidronate or zoledronic acid, in accordance with FDA-approved labeling. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly but there is no evidence upon which to base a recommendation for time intervals. In contrast to multiple myeloma patients, there currently is no data to support routine assessments for albuminuria in breast cancer patients.
Biochemical markers	The use of the biochemical markers to monitor bisphosphonate use is not suggested for routine care	No change
Duration of therapy	The panel suggests that once initiated, intravenous bisphosphonates be continued until evidence of **substantial decline** in a patient's general performance status. The panel stresses that clinical judgment must guide what is a substantial decline. There is no evidence addressing the consequences of stopping bisphosphonates after one or more adverse skeletal events.	No change

Table 1. Summary of Guidelines (continued)

Specific Guideline	2000 Recommendation	2003 Recommendation
Role in control of pain secondary to bone metastases	The Panel recommends that current standards of care for cancer pain, analgesics and local radiation therapy should not be displaced by bisphosphonates. Intravenous pamidronate is recommended in women with pain as a result of osteolytic metastasis to relieve pain when used concurrently with systemic chemotherapy and/or hormonal therapy, because it was associated with a modest pain control benefit in controlled trials.	The Panel recommends that the current standards of care for cancer pain management must be applied throughout bisphosphonate therapy and is required by good clinical practice. These standards of care for pain management include analgesics, corticosteroids, interventional procedures, nonsteroidal anti-inflammatory agents, systemic radiopharmaceuticals, and local radiation therapy. Among other therapeutic options, intravenous pamidronate or zoledronic acid may be of benefit among women with pain caused by bone metastases to relieve pain when used **concurrently** with systemic chemotherapy and/or hormonal therapy, because it was associated with a modest pain control benefit in controlled trials.
	There is insufficient evidence to support a role for intravenous bisphosphonates as an adjunctive therapy to radiation therapy in women with pain as a result of metastatic bone disease when systemic chemotherapy and/or hormonal therapy **is not** being employed. The role of bisphosphonates vis-à-vis radiation therapy as the sole therapy in this setting has not been determined. In women already treated with local radiotherapy who have persistent or recurrent pain, bisphosphonates are an attractive but little studied salvage therapy.	No change
The role of bisphosphonates if no radiographic evidence of bone metastases		
Extraskeletal metastases without evidence of bone metastases	Starting bisphosphonates in women without evidence of bone metastases even in the presence of other extra-skeletal metastases is not recommended. This clinical situation has not been studied using intravenous bisphosphonates and should be the focus of new clinical trials.	No change
Bisphosphonates as adjuvant therapy	Inconsistent, evolving data have been found in studies with bisphosphonate use in the adjuvant setting to prevent osseous metastases. Starting bisphosphonates in women at any stage of their nonosseous disease, outside of clinical trials, despite a high risk for future bone metastasis is currently not recommended.	No change
Bone health in women with a history of breast cancer		
Osteoporosis prevention	Oral bisphosphonates are one of several potential options that can be used for preservation of bone density in premenopausal women with treatment-induced (usually secondary to chemotherapy) menopause.	Most women with newly diagnosed breast cancer are at risk of osteoporosis either because of their age or their breast cancer treatment. Oncology professionals, especially medical oncologists, need to take an expanded role in the routine and regular assessment of these women's bone health. The panel recommended an algorithm for patient management to maintain bone health.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; FDA, Food and Drug Administration.

years. Although the type of systemic adjuvant therapy was not prescribed, the categories of no adjuvant therapy, chemotherapy, tamoxifen, or both chemotherapy and tamoxifen were balanced between the arms. The treatment arms were also balanced by stage and nodal status, and median follow-up was 5.5 years. Overall for the entire follow-up period, there was a nonsignificant decrease in the incidence of bone metastases (HR, 0.77; 95% CI, 0.56 to 1.08; $P = .127$) and there was no difference in the frequency of nonosseous metastases. During the 2 years of clodronate use, bone metastases were significantly lower in the group receiving clodronate compared with placebo (2.3% *v* 5.2%; $P = .016$); however, at 5 years follow-up, bone metastasis were no longer significantly different between the two treatment arms (12% *v* 15%; $P = .107$). No effect was observed on visceral sites of metastasis (17% *v* 20%; $P > .05$). Overall survival, which was not a primary

Table 2. Adjuvant Trials of Clodronate

	Diel Study[26]	Powles Study[25]	Saarto Study[24]
Design			
Enrollment	1990-1995	1989-1995	1990-1993
Sample size	302 patients	1069 patients	299 patients
Staging	50% node positive, 75% ER positive	37% node positive, 64% ER positive	100% node positive
Entry			
Pretreatment x-rays	Not reported	Not reported	100% bone scintigraphy
Planning			
End point assessment schedule	Every 3-4 m first 2 years	Every 3 m first year; every 6 m 2-5 years	Every 4 to 6 m
Preplanned primary endpoint	Development of bone metastases	Development of bone metastases	Development of bone metastases
Prestudy power calculation	10% absolute difference in bone metastases	25% reduction in bone metastases at 60 m; 50% reduction in bone metastases on treatment	Uncertain. 10-15% absolute reduction in bone metastases
Radiographs read blind and independently	Yes	Not reported	Not reported
Intent to treat analysis	Yes	Yes	Yes, secondary
Follow-up			
Imaging completed during follow-up	Annual chest x-ray, bone scan, liver ultrasound; x-rays if clinically indicated	At 24 m, 60 m and as indicated	Scintigraphy 1, 2, 3 and 5 years, x-rays if clinically indicated
Bony metastases			
Primary endpoint	8% c *v* 17% p at 36 m; $P = .003$	3.8% c *v* 6.7% p at 24 m (while on treatment); $P = .016$	Not reported
At 5 years	14% c *v* 24% p; $P = .04$	11.1% c *v* 10.2% p; $P = .127$	21% c *v* 17% p
Survival			
Primary end point	4% c *v* 15% p at 36 m; $P = .001$	92.7% c *v* 92.4% p at 24 mo; $P = .21$	
At 5 years	91% *v* 77% p; $P = .002$	82.9% *v* 79.3% p; $P = .047$	70% c *v* 83% p; $P = .009$
Summary			
Relative risk	0.70 (calculated) at 36 m	0.44 (0.22-0.86); $P = .016$ at 2 years (on treatment)	NA, increased risk
	0.41 (calculated) at 5 years	0.77 (0.56-1.08); $P = .127$ at 5 years	NA, increased risk

Abbreviations: c, clodronate; p, placebo; ER, estrogen receptor; m, months; NA, not applicable.

end point, was significantly improved in the clodronate arm (82% *v* 76%; 95% CI, 0.59 to 1.00; $P = .047$). Further evaluation in a larger study is needed (see National Surgical Adjuvant Breast and Bowel Project [NSABP] B34 discussion).

Saarto et al[24] reported results of a double-blind trial of 299 women with node-positive breast cancer who were randomly assigned to receive clodronate 1,600 mg/d or placebo for 3 years. All women received adjuvant therapy; premenopausal women received chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) and postmenopausal women received antiestrogens. All patients were followed for 5 years. There was no significant difference in the frequency of bone metastases between the two arms, with 26% of patients in the clodronate group and 18% in the control group developing osseous metastases. The incidence of nonosseous metastases was significantly higher in the clodronate arm (43% *v* 25%; $P = .0007$). Both DFS and OS were significantly worse in the clodronate arm (DFS, 56% *v* 71%; $P = .007$; OS, 70% *v* 83%; $P = .009$). This apparent adverse effect of clodronate remained significant in the multivariate analyses after adjustment for other prognostic factors, including number of lymph nodes, tumor size, and hormone receptor status.

Therefore, there are three phase III prospective trials that address the role of adjuvant clodronate, two of which yielded favorable results and one that demonstrated an adverse impact. Given that the three trials are inconsistent, it remains uncertain whether bisphosphonates are beneficial and, if so, what is the optimal agent, route of therapy, dose, schedule, and duration of therapy. The intriguing but contradictory results of these three adjuvant bisphosphonate studies highlight the need for further investigation to determine whether bisphosphonates can influence the development of bone metastases and improve survival in early stage breast cancer.

The ongoing NSABP trial B34, in which 2,400 early stage breast cancer patients are randomly assigned to adjuvant clodronate or placebo, is a critical and definitive trial regarding clodronate. This trial, which should complete its accrual in 2003, will have its final analysis at 460 events (expected after 7 years) and is designed to detect a 23% reduction in the hazard rate for the primary end point of DFS. Additionally, the North American Intergroup will conduct an adjuvant bisphosphonate trial (S0307) comparing oral clodronate to newer, more potent bisphosphonates (risedronate, zoledronic acid). Finally, there is a growing role for the use of bisphosphonates in the prevention and treatment of osteoporosis (see next section on bone health), a major treatment issue in women undergoing systemic adjuvant therapy. More breast cancer patients will likely be receiving bisphosphonates for this indication in the

future, which will potentially confound the interpretation of the adjuvant trial literature.

At present, adjuvant clodronate cannot be recommended as a standard of care for any women about to undergo systemic adjuvant therapy, yet these trials provide provocative data worthy of establishing hypotheses for prospective studies.

BONE HEALTH IN WOMEN WITH A HISTORY OF BREAST CANCER

Osteoporosis Prevention

2000 recommendation. Oral bisphosphonates are one of several potential options that can be used for preservation of bone density in premenopausal women with treatment-induced (usually secondary to chemotherapy) menopause.

2003 recommendation. Most women with newly diagnosed breast cancer are at risk of osteoporosis due to either their age or their breast cancer treatment. Oncology professionals, especially medical oncologists, need to take an expanded role in the routine and regular assessment of these women's bone health. The Panel recommended an algorithm for patient management to maintain bone health.

Evidence Summary

Osteoporosis is an increasingly common problem in women with diagnosed breast cancer. Evidence now supports strategies for osteoporosis screening, prevention and therapy in otherwise healthy women. Current information regarding osteoporosis prevention and therapy is outlined in the next section. This outline summarizes the additional risks of osteoporosis development associated with a breast cancer diagnosis. The available information on osteoporosis prevention and therapy in breast cancer patients is outlined and, largely by inference, a strategy for osteoporosis screening, prevention, and therapy for breast cancer patients without evidence of bone metastases is described.

Women with a breast cancer diagnosis are at increased risk for osteoporosis and fracture. In one study, the presence of even localized breast cancers influenced fracture risk.[28] Vertebral fracture risk was greater in breast cancer patients with resected, localized disease (odds ratio [OR], 4.7; 95% CI, 2.3 to 9.9) and 23 times greater in breast cancer patients with soft tissue metastasis without evidence of bone metastasis (OR, 22.7; 95% CI, 9.1 to 57.1) compared with women with no cancer. Confirmatory studies addressing this risk will soon be reported.

Background. Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.[29] Bone strength reflects the integration of bone density and bone quality. The World Health Organization operationally defines osteoporosis as a bone density that is 2.5 standard deviations (expressed as a *t*-score) below peak bone mass or the mean bone density for young white adult women.[30] Osteopenia, or low bone mass, is defined as a *t*-score of -1 to -2.5 below the normal score for young adult women. The pathogenesis of osteoporotic fractures is complex, with a number of identified risk factors. Among these are modifiable factors (low bone mass and poor bone quality, smoking, caffeine intake, inactive lifestyle, muscle weakness, low body weight and weight loss, low calcium and vitamin D intake, and low estrogen levels), as well as unmodifiable ones (older age, female sex, white or Asian race, maternal history of fractures, height, late menarche, impaired mental status, and hip geometry). Fall-related factors include a history of falls, poor balance, impaired visual function, and use of long-acting sedatives. A number of genes thought to contribute small to moderate effects on osteoporosis risk have also been identified.[31]

Low bone mineral density (BMD) and history of fracture are two of the strongest fracture risk factors. One SD decrease in hip BMD is associated with a 2.6-fold increase in hip fracture risk.[32] The 5-year absolute risk of a vertebral fracture at age 65 (*t* score $= -2.5$) is about 8%; this increases to about 15% by age 85.[32] Women with a prevalent vertebral fracture are two to four times more likely to experience a new vertebral fracture[33,34] and twice as likely to experience a hip fracture.[34]

Recommendations for osteoporosis screening. The United States Preventive Services Task Force (USPSTF) recently released recommendations on when to begin BMD screening for osteoporosis; age $\geq$ 65 years for all women and at age 60 for women at increased osteoporosis risk.[35] The exact risk factors that should trigger screening were not specified, but low body weight ($<$70 kg) and prior fracture history are strong risk predictors. Based on limited evidence, USPSTF made no recommendation regarding routine screening in any other women.

General principles of osteoporosis prevention and therapy. Preventing osteoporotic fractures can be achieved by maximizing peak skeletal mass, preventing or slowing rates of bone loss, and preventing falls. Fundamental measures for bone health include adequate calcium intake (1,200 mg/d), and vitamin D intake (400 to 800 U), exercise, and avoidance of smoking. Women who should receive osteoporosis therapy include those with prior fragility fractures, as well as women with a BMD *t* score ≤ -2.5.[36] Treatment of women without fractures but who have borderline low BMD (*t* score < -1.0) and other risk factors is controversial and should be decided on an individual basis.

The Osteoporosis Research Advisory Group (ORAG) has provided a comprehensive review of the randomized trials of osteoporosis therapies.[37] Vitamin D (hydroxylated), calcitonin, raloxifene, the bisphosphonates, etidronate, risedronate, and alendronate all reduced vertebral fractures with the strongest data supporting alendronate and risedronate. Only alendronate and risedronate significantly reduced nonvertebral fractures. The particular issues relevant to women with breast cancer are summarized in Table 3. In postmenopausal women, tamoxifen had modest influence on BMD[38,39] and fracture risk,[40] but is not considered a stand-alone osteoporosis therapy. Raloxifene is approved for osteoporosis prevention and therapy exclusively in postmenopausal women. There are reservations regarding use of raloxifene following 5 years of tamoxifen adjuvant therapy because raloxifene has limited activity against advanced breast cancer when used after tamoxifen,[41]and 10 years of tamoxifen has been associated with more recurrences than stopping tamoxifen after 5 years.[42] Other agents not currently approved by the FDA for osteoporosis prevention may also

Table 3. Therapies Available for Osteoporosis Prevention and Therapy: Approved by US FDA

Therapy	Dosage	Common Side Effects	Issues for Use in Breast Cancer Patients
FDA approved bisphosphonates			
Alendronate	5 mg PO daily	Upper GI irritation, myalgias and arthralgias	None
Prevention and treatment	35 PO weekly 10 mg PO daily 70 PO weekly		
Risedronate			None
Prevention and treatment	5 mg PO daily 35 PO weekly		
Selective estrogen receptor modulator			
Raloxifene			
Prevention and treatment	60 mg PO daily	Common: Hot flashes, leg cramps; rare: deep vein thromboses	Cross resistance with tamoxifen; not recommended after tamoxifen
Parathyroid Hormone (synthetic)			
Teriparitide	20 U SQ daily	Common: dizziness, leg cramps; rare: hypercalcemia	Not recommended; Should not be used in patients at increased risk of bone metastases or hypercalcemia (due to osteosarcoma development in animal models)
Estrogen plus progestin combination	Varies		
Five combination agents			
Prevention only		Common: breast tenderness, vaginal bleeding; life threatening: CHD, stroke, PE, breast cancer	Not recommended in patients with a breast cancer diagnosis when used for osteoporosis prevention
Estrogens			
Nine agents			
Prevention only	Varies	Common: breast tenderness, vaginal bleeding; life threatening: CHD, stroke, PE, breast cancer	Not recommended in patients with a breast cancer diagnosis when used for osteoporosis prevention
Calcium	1200 mg/d	Constipation, bloating, gas	None
Vitamin D	400-600 mg	None	None
Calcitonin nasal spray	200 U one nostril/day	Rhinitis	None

Abbreviations: FDA, Food and Drug Administration; PO, orally; SQ, subcutaneous; GI, gastrointestinal; CHD, coronary heart disease; PE, pulmonary embolism.

influence fracture risk and include tibolone,[43] strontium,[44] and bisphosphonates clodronate, ibandronate, pamidronate, tiludronate,[45] and zoledronic acid. This latter bisphosphonate, in one randomized trial, reversed osteoporosis BMD with a 4 mg intravenous annual infusion.[46]

After the ORAG report was released, teriparitide,[37] a synthetic parathyroid hormone, was approved for osteoporosis therapy. However, because this drug was associated with osteosarcoma development in animal studies, it is not recommended for use in women with diagnosed breast cancer. In addition, the recent report indicating more overall risk versus benefit for estrogen plus progestin use, including increased breast cancer risk, makes use of menopausal hormones for osteoporosis prevention in breast cancer patients especially problematic.[47]

Postmenopausal adjuvant therapy. Trends in adjuvant hormonal therapy indicate that osteoporosis will become a greater clinical problem in the future. The relative percentage of breast cancer that is estrogen receptor–positive increases with age and peaks at approximately 75% in women over 70 years of age.[48] For such women with advanced breast cancer, use of progestins (largely felt to be neutral with respect to bone density[49]) is being replaced by aromatase inhibitors, which are associated with bone loss and increased fracture risk.[50] In the adjuvant setting, the aromatase inhibitor anastrozole is approved by the FDA for postmenopausal women with early stage receptor-positive breast cancer.[51,52] When used in that setting, it replaces tamoxifen, a drug associated with increased bone density and reduced fracture risk.[40] In the large anastrozole, tamoxifen, alone or in combination (ATAC) trial in postmenopausal women with early stage breast cancer, anastrozole significantly increased fracture risk compared with tamoxifen (incidence of 7.1% seen on anastrozole *v* 4.1% on tamoxifen after a mean of 37 months follow-up; OR, 1.34; 95% CI, 1.22 to 1.57).[51] In a subset of 300 ATAC patients who had baseline and 1-year later biochemical markers of bone turnover and bone mineral density (BMD) assessments, anastrozole patients had increased bone resorption markers and decrease in spine and hip BMD, and in the tamoxifen patients, the converse occurred. Indirect comparison suggest about a third of the excess fracture risk seen with anastrozole in the ATAC trial is related to absence of a tamoxifen effect.[53]

Although raloxifene is approved for osteoporosis prevention and therapy, its use following 5 years of tamoxifen adjuvant therapy is not recommended. This is based on the fact that raloxifene and tamoxifen are similar agents and 10 years of

tamoxifen use has been associated with more recurrences and deaths than 5 years of tamoxifen.[42] In addition, laboratory studies show that raloxifene may stimulate tamoxifen-dependent cells.[54] Concurrent use of raloxifene and aromatase inhibitors is not recommended based on the adverse effect of combining tamoxifen with anastrozole in the ATAC trial.[51]

Premenopausal therapy. Regardless of receptor status, many premenopausal women with early stage breast cancer are at risk of chemotherapy associated premature menopause,[55-57] which results in rapid bone loss comparable to that seen with surgical oophorectomy (7.7% loss in lumbar spine BMD in one report).[57] Use of adjuvant taxanes can further increase the frequency of premature menopause.[58] Premenopausal women treated with ovarian suppression without concurrent tamoxifen are at similar levels of bone loss risk. Concurrent tamoxifen use in this setting may not be protective since some studies have suggested that tamoxifen itself is associated with loss of bone density in premenopausal women.[39]

Bisphosphonates in combination with adjuvant therapy in breast cancer patients without bone metastases. The effect on bone mineral density of bisphosphonates with hormonal or cytotoxic chemotherapy is being evaluated in comparative trials. In a small trial of 120 postmenopausal breast cancer patients without skeletal metastases, women were randomly assigned to one of two selective estrogen receptor modulators (SERMs), either tamoxifen or toremifene and, in a factorial design, had a second randomization to oral clodronate 1,600 mg daily or control (no bisphosphonate). At 2 years, clodronate together with a SERM markedly increased lumbar spine BMD by 2.9% ($P = .001$) while patients receiving the SERM alone did not significantly increase BMD.[59]

For breast cancer patients given adjuvant CMF chemotherapy, significantly less BMD loss occurred in women randomly assigned to oral clodronate compared with placebo.[60] Currently, there is only one report on the efficacy of oral bisphosphonates FDA approved for osteoporosis therapy in the United States in a breast cancer population at risk for bone loss. In a 52 patient randomized trial, the bisphosphonate risedronate taken as 30 mg per day for 2 weeks followed by 10 weeks of no drug, was shown to prevent bone loss in young women with breast cancer and premature chemotherapy induced menopause.[61]

In a promising preliminary report, premenopausal breast cancer patients receiving goserelin plus anastrozole or goserelin plus tamoxifen were randomly assigned to the bisphosphonate zoledronic acid (4 mg IV q 6 months) or placebo. After 6 months, those receiving zoledronic acid had significantly higher lumbar spine BMD ($P < .0001$).[53] Completion of this trial is needed before the Panel can make a specific recommendation. Currently, there are no reports of the use of calcium and vitamin D in breast cancer patients free of bone metastases.

Bone health summary. In otherwise healthy women, a strong body of evidence supports a strategy of early detection and therapy of osteoporosis. Similar recommendations can be applied to breast cancer patient management, as shown in Figure 1. Breast cancer patients identified by their history to be at high risk for osteoporosis should be evaluated by BMD. As in women without breast cancer, subsequent interventions are guided by BMD results. Current evidence is insufficient to support intravenous pharmacologic interventions to maintain normal BMD in any subgroup of breast cancer patients without bone metastases.

Breast cancer patients found to have osteoporosis based on BMD results (t score −2.5 or lower) should have pharmacologic therapy initiated with an agent demonstrated to have efficacy. There is currently insufficient evidence to recommend a particular agent in this category. Breast cancer patients found to have osteopenia based on BMD results (t score between −1 and −2.5) should have their therapy individualized, but current evidence cannot support routine intervention with bisphosphonates for this group.

COMMENTARY: PUBLIC POLICY AND COST-UTILITY IMPLICATIONS

Prior cost-effectiveness analyses have suggested that the cost-savings from bisphosphonates and/or radiation in reducing bone complications were insufficient to offset the costs associated with the bisphosphonates and their delivery.[62-64] Since 2000, there have been new cost-effectiveness assessments of bisphosphonates in breast cancer.

There is new retrospective data indicating that a reduction in medical services is probably the case with intravenous bisphosphonates, but that the initial characteristics of patients receiving pamidronate substantially differ. The chart review study involving 12 community U.S. oncology sites compared women who initiated pamidronate within 3 months (early) of bone metastasis diagnosis or after 3 months (late) of diagnosis with patients who never (none) received pamidronate between July 1996 and April 1999;[64] 295 patients were identified. Patients receiving early pamidronate were more likely to have multiple bone lesions, a serious initial event or hypercalcemia. Pamidronate-treated patients needed less radiotherapy and the duration of hospitalizations were about 50% shorter than nonpamidronate patients.

With the recent approval of zoledronic acid in the United States, the decision facing most oncologists will be whether to switch from pamidronate to zoledronic acid. In 2001, generic pamidronate became available. In 2003, there are at least four suppliers of generic pamidronate. In an ideal world, competition would drive down the price of pamidronate; however, current US average wholesale prices of pamidronate have changed minimally since the introduction of generic versions.

Pamidronate's longer infusion time compared with zoledronic acid (2 hours *v* 15 minutes) is associated with an opportunity for lower cost to the patient (their time), the cancer location (use of infusion chair), and extra staff time (reflected in common procedural terminology codes). A time and motion study at three outpatient chemotherapy infusion sites participating in the zoledronic acid versus pamidronate clinical trial found an average visit time for zoledronic acid patients was 1 hour, 6 minutes, compared to 2 hours, 52 minutes for pamidronate patients.[65] From the infusion center perspective, the opportunity benefit for zoledronic acid was an average increase in 1.8 chairs per day available for other patients.

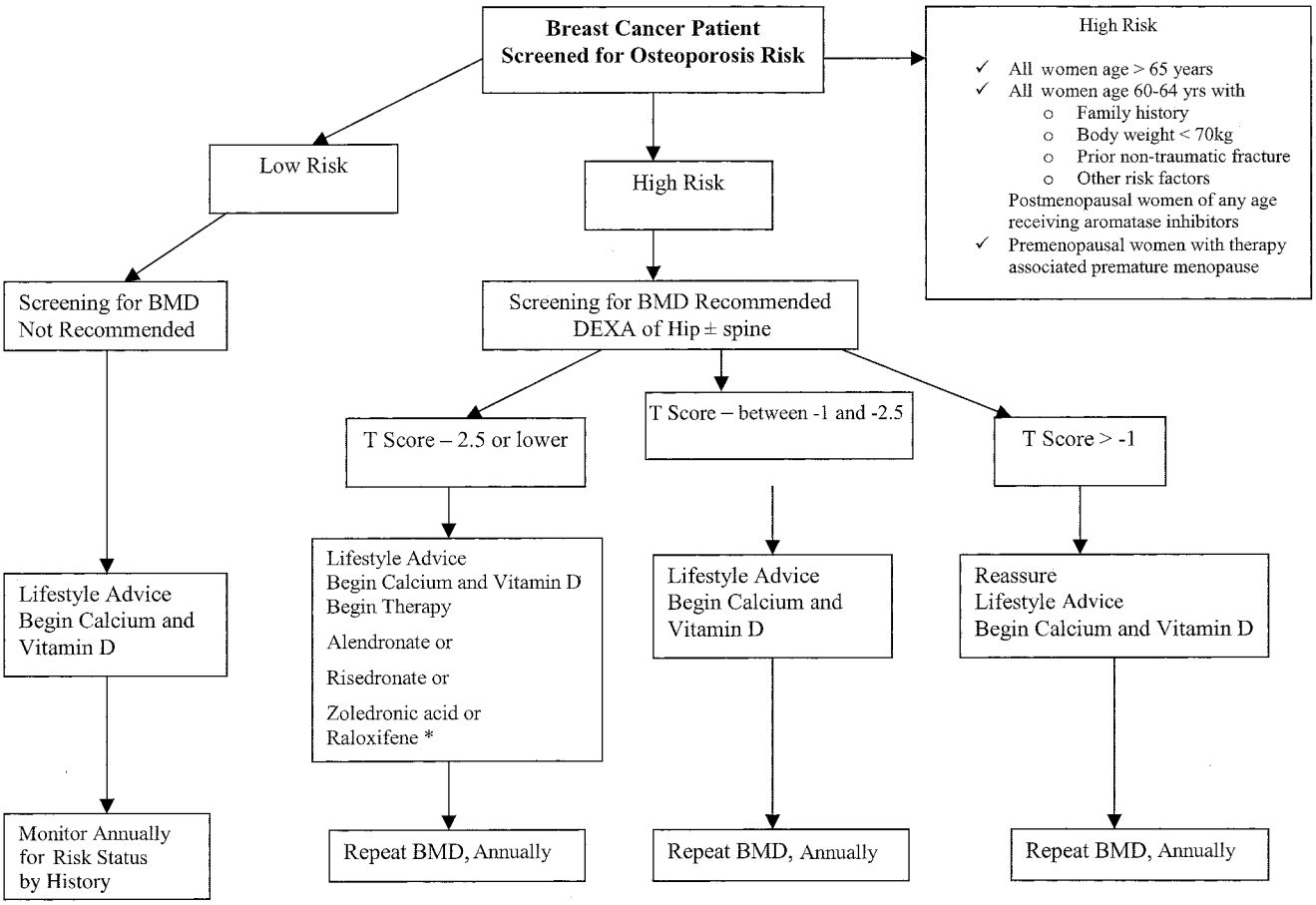

Fig 1. Recommended management strategy for patients with diagnosed nonmetastatic breast cancer. This management strategy is largely based on influence from results in non-breast cancer populations. BMD, bone mass density; DEXA, dual energy x-ray absorptiometry bone scan.

The choice of bisphosphonates is broader in number and delivery method (oral *v* intravenous) outside the U.S. Where oral clodronate is available, the price difference between available bisphosphonates is commonly minimal, and the absolute cost for any bisphosphonate is much lower per standard treatment interval. Pamidronate and zoledronic acid have acquisition prices in most of Europe that are 40% to 70% less than the U.S. Therefore, each country must make its own relative cost benefit assessment.

ONGOING AND FUTURE RESEARCH

Ongoing and future clinical trials with bisphosphonates in breast cancer include metastatic trials investigating optimal use of approved agents, as well as promising new drugs, adjuvant trials evaluating a potential prevention role for bisphosphonates, and studies looking at minimizing cancer treatment-related loss of bone mineral density.

Metastatic breast cancer. In metastatic breast cancer, the major unanswered questions listed in the 2000 guidelines regarding bisphosphonates remain unanswered and uninvestigated. These include the optimal drug, dosing, route of delivery, duration of therapy, timing of initiation of drug, and toxicity monitoring. New amino-bisphosphonates are in varying phases of clinical development.

Ibandronate, a third generation bisphosphonate, is approved in intravenous form for treatment of hypercalcemia of malignancy in over 50 countries outside the United States. Phase III studies of both oral and intravenous ibandronate compared with placebo have recently been completed.[66,67]. In 2002 and 2003, the Panel made written requests to Hoffman LaRoche (Nutley, NJ) for data. No responses were received. Data on the oral ibandronate studies were presented at the ASCO meeting in 2003.[67](This summary is based on published reports only). A pooled analysis of two randomized, double blind, placebo-controlled phase III trials of oral ibandronate (50 mg and 20 mg) versus placebo was performed among breast cancer patients with bone metastases. Significant improvements in the primary end point and the skeletal morbidity rate were observed for both oral doses of ibandronate when compared with placebo. A supplemental application was filed in late 2002 with the European Agency for the Evaluation of Medicinal Products for the treatment of bone metastases in breast cancer patients with both oral and intravenous versions of ibandronate. The Southwest Oncology Group (SWOG) trial S0308 will evaluate oral ibandronate (50 mg daily) in breast cancer patients with bone metastases as compared to zoledronic acid (4 mg intravenous monthly), with time to first skeletal-related event as the primary study end point.

Adjuvant breast cancer. The intriguing but contradictory results of the three adjuvant bisphosphonate studies reported to date highlight the need for further investigation. The NSABP protocol B34 is evaluating oral clodronate for 3 years versus placebo in addition to standard treatment in 2,400 patients with stage I or II breast cancer. At the closure of NSABP B34, the North American Intergroup will initiate a 6,000 patient, three-arm adjuvant bisphosphonate trial (S0307, lead by SWOG) comparing 3 years of oral clodronate to two newer, more potent bisphosphonate agents, oral risedronate and intravenous zoledronic acid. A multinational Adjuvant Zoledronic Acid Reduce Recurrence study, also soon to begin accrual, is a prospective, randomized, open-label trial to determine if adjuvant treatment with zoledronic acid plus standard systemic therapy is superior to systemic therapy alone in improving DFS.

If benefit for bisphosphonates is proven in the adjuvant breast cancer setting, we will need to carefully address the optimal agent, dose, schedule, and duration of therapy. Whether doses used in metastatic disease are required for prevention, or whether lower doses would suffice, is unknown. It is unclear whether adjuvant bisphosphonates should be given continuously and orally, or whether intermittent intravenous therapy would be preferable. The optimal duration of therapy is also unknown, with current studies suggesting that 2 years is an insufficient treatment length. Long-term follow-up will be needed to determine if bisphosphonates are actually able to prevent or merely delay bone lesions.

Incorporated into the upcoming adjuvant bisphosphonate trials are correlative studies investigating the use of markers to select high-risk women. Ultimately, we would hope to determine which breast cancer patients might benefit most from adjuvant bisphosphonates by evaluating tumor characteristics, urine or serum markers, or bone marrow findings that predict who is at highest risk for bone recurrence.

Cancer treatment-related bone loss. Irrespective of the development of bone metastases, it is possible that all early stage breast cancer patients could benefit from bisphosphonates in the form of preservation of bone density. Adjuvant aromatase inhibition in postmenopausal patients and ovarian suppression in premenopausal patients are the subject of ongoing studies.

The final report of the Austrian Breast Cancer Study Group randomized trial of zoledronic acid in premenopausal women treated with hormonal therapy (discussed in the osteoporosis section) is eagerly anticipated.

The international pharmaceutical company-sponsored Zometa/Femera Adjuvant Synergy Trial study is an open-label, randomized, multicenter study evaluating the use of zoledronic acid in the prevention of cancer treatment-related bone loss in postmenopausal breast cancer patients receiving letrozole as adjuvant therapy. The International Breast Cancer Intervention Study II comparing anastrozole to placebo in women at high risk of developing breast cancer, and tamoxifen to anastrozole in ductal carcinoma in situ, has subprotocols including a bisphosphonate examining the effects of risedronate on prevention of bone loss associated with anastrozole. CALGB protocol 79809 is a phase II trial of intravenous zoledronic acid for the prevention of bone loss among localized breast cancer patients with chemotherapy-induced ovarian failure.

Other osteoclast-targeted therapies. Additionally, non-bisphosphonate compounds that interfere with bone metabolism are under investigation in breast cancer patients with bone metastases. Agents of interest include anti-RANK ligand pathway-targeted therapy, and anti-parathyroid hormone-related peptide antibodies.

ACKNOWLEDGMENT

The Expert Panel wishes to express its gratitude to Drs Harold Burstein and Gabriel N. Hortobagyi for their thoughtful reviews of earlier versions of these guidelines.

APPENDIX
Bisphosphonates in Breast Cancer Expert Panel

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

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