Evidence-based Series 1-11 Version 2.2002: TO BE UPDATED

Use of Bisphosphonates in Women with Breast Cancer

Members of the Breast Cancer Disease Site Group
A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Evidence-based Series (EBS) 1-11 Version 2.2002 requires an UPDATE. The EBS was reviewed in 2012, and the Breast Cancer Disease Site Group (DSG) made the decision to UPDATE it in 2 separate documents (nonmetastatic and metastatic).


EBS 1-11 Version 2.2002: TO BE UPDATED consists of the following 4 sections:
1. Guideline Report Overview
2. Summary
3. Full Report
4. Document Assessment and Review Tool

and is available on the CCO website (http://www.cancercare.on.ca)
PEBC Breast Cancer DSG page at:
http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/

Release Date: May 15, 2012

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PEBC Report Citation (Vancouver Style): Members of the Breast Cancer Disease Site Group. Use of bisphosphonates in women with breast cancer. Clemmons M, Agbassi C, reviewers. Toronto (ON): Cancer Care Ontario; 2012 May 15 [To be updated 2012 Feb]. Program in Evidence-based Care Evidence-Based Series No.: 1-11 TO BE UPDATED.

Evidence-based Guideline 1-11: TO BE UPDATED

Use of Bisphosphonates in Women with Breast Cancer

Guideline Report History

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Evidence-based Series 1-11: TO BE UPDATED

Use of Bisphosphonates in Women with Breast Cancer

Guideline Review Summary

Review Date: February 13, 2012

The 2004 guideline recommendations require UPDATE

This means that the DSG/GDG will rewrite the guideline at the earliest opportunity. Until then the recommendations remain of some use in clinical decision making

OVERVIEW
Evidence-based Series History
This guidance document was originally released by Cancer Care Ontario’s Program in Evidence-based Care in 1998. A second version was released in December 2002 and was updated in April 2004. In January 2012, the PEBC guideline update strategy was applied and the new document to be updated released in February 2012. The summary and the full report in this version are the same as April 2004 version.

Update Strategy
Using the Document Assessment and Review Tool (at the end of this report), the PEBC update strategy includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS
Questions Considered
1. Should bisphosphonates be used to reduce pain, reduce the likelihood of skeletal events other than hypercalcemia (i.e., fractures, requirement for radiation therapy, surgery), improve quality of life, or improve survival in women with bone metastases due to breast cancer?
2. Should bisphosphonates be used to reduce the likelihood of bone metastases or to improve survival in women with breast cancer that is locally advanced or metastatic to sites other than bone?
3. Should bisphosphonates be used to reduce the risk of bone metastases or improve survival in women with early stage breast cancer?

Additional Questions Considered
4. Can we identify patients at different risks of skeletal-related events so that the frequency of administration of bisphosphonates can be adjusted to reflect their use in the modern era?
5. Should bisphosphonates be used to reduce the risk of cancer therapy induced bone loss in women with early stage breast cancer?

Literature Search and New Evidence
The new search (March 2004 to March 2011) yielded 33 relevant new publications representing two guidelines, six meta-analyses and 20 RCTs were found. Initial publications of five of the RCTs were already included in the original document. Brief results of these publications are shown in the Document Assessment and Review Tool at the end of this report.

Impact on Guidelines and Its Recommendations
The new data supports existing recommendations but the Breast Cancer DSG members did not reach a consensus on endorsement because the current recommendations do not cover all relevant subjects. Moreover, the volume and content of the newly identified evidence is so extensive that a simple update could not be achieved using the document assessment and review tool. The PEBC and the Chairs of the Breast Cancer DSG decided that the 2004 recommendations on the use of bisphosphonates in women with breast cancer require an UPDATE.

With regard to future guideline production by the Breast DSG:
- It would be useful to produce a guideline on all bone-targeted agents, not just bisphosphonates - particularly of interest is the new agent denosumab.
- Since a vast amount of literature is expected on bone-targeted agents, it would be easier to handle if produced as two separate guidelines for:
  - early-stage breast cancer
  - metastatic breast cancer
- It would also be useful to have another guideline to address the use of bone-targeted agents for cancer-therapy induced bone-loss.
Use of Bisphosphonates in Women with Breast Cancer

D Warr, M Johnston, and members of the Breast Cancer Disease Site Group


Report Date: April 2004

SUMMARY

Guideline Questions
- Should bisphosphonates be used to reduce pain, reduce the likelihood of skeletal events other than hypercalcemia (i.e., fractures, requirement for radiation therapy, surgery), improve quality of life, or improve survival in women with bone metastases due to breast cancer?
- Should bisphosphonates be used to reduce the likelihood of bone metastases or to improve survival in women with breast cancer that is locally advanced or metastatic to sites other than bone?
- Should bisphosphonates be used to reduce the risk of bone metastases or improve survival in women with early stage breast cancer?

Target population
These recommendations apply to women with breast cancer.

Original 2002 Recommendations
- Women with breast cancer who have bone metastases should be offered treatment with oral clodronate or intravenous pamidronate.
  - An exception may be patients with a short expected survival (i.e., less than six months), who have well controlled bone pain.
  - Patients who have difficulty tolerating oral medications (e.g., those with nausea/vomiting or esophagitis) should be offered intravenous pamidronate.
  - Intravenous zoledronate is an alternative to pamidronate when a shorter infusion time (15 minutes) is important.
  - Intravenous clodronate has not been examined for its ability to reduce morbidity from bone metastases with long-term use. When clodronate is used for this purpose, the oral route is recommended.
- In patients with bone metastases and pain, treatment with pamidronate, zoledronate, or clodronate may be a useful adjunct to conventional measures for pain control.
Bisphosphonates are not recommended to prevent bone metastases or improve survival in women with locally advanced breast cancer or non-skeletal metastases.

Current evidence is insufficient to support the use of bisphosphonates as adjuvant therapy to either prevent skeletal events or improve survival in women with early-stage breast cancer.

Updated 2004 Recommendations
Slight modifications were made to the above recommendation. These are detailed in the PRACTICE GUIDELINE section of the full report.

- Women with breast cancer who have bone metastases should be offered treatment with oral clodronate, intravenous pamidronate, or intravenous zoledronate.
  - An exception may be patients with a short expected survival (i.e., less than six months), who have well-controlled bone pain.
  - Patients who have difficulty tolerating oral medications (e.g., those with nausea/vomiting or esophagitis) should be offered intravenous pamidronate or zoledronate.
  - Intravenous zoledronate may be preferable to pamidronate when a shorter infusion time (15 minutes versus two hours, respectively) is important.
  - Intravenous clodronate has not been examined for its ability to reduce morbidity from bone metastases with long-term use. When clodronate is used for this purpose, the oral route is recommended.

- In patients with bone metastases and pain, treatment with pamidronate, zoledronate, or clodronate may be a useful adjunct to conventional measures for pain control.

Bisphosphonates are not recommended to prevent bone metastases or improve survival in women with locally advanced breast cancer or non-skeletal metastases.

Current evidence is insufficient to support the use of bisphosphonates as adjuvant therapy to either prevent skeletal events or improve survival in women with early-stage breast cancer.

Qualifying Statements

- There is no evidence from clinical trials that address the optimal duration of bisphosphonate use.
- There are no data on the efficacy of bisphosphonates in men with breast cancer, but men have participated in randomized trials of bisphosphonates for multiple myeloma. Since there is no evidence to suggest that the benefit detected in multiple myeloma trials is gender specific, it is reasonable to recommend the use of bisphosphonates in men with breast cancer that is metastatic to bone.

Methods
The literature was searched to August 2002 using MEDLINE, the Cochrane Library, practice guideline Internet sites, abstracts published in the proceedings of the annual meeting of the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium, and bibliographies. The original literature search was updated to February 2004 using MEDLINE, the Cochrane Library, conference proceedings from the American Society of Clinical Oncology (2003) meeting and the San Antonio Breast Cancer Symposium (2002-2003), and bibliographies. Relevant Web sites were searched for new evidence-based practice guidelines.

Evidence was selected and reviewed by one member of the Practice Guidelines Initiative Breast Cancer Disease Site Group. This practice-guideline report was reviewed and approved by the Breast Cancer Disease Site Group, which comprises surgeons, medical
oncologists, radiation oncologists, pathologists, a medical sociologist, a research methodologist, a nurse representative, and a patient representative.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the practice guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Original 2002 Key Evidence

- Sixteen randomized trials evaluated the addition of oral or intravenous bisphosphonates to chemotherapy or hormonal therapy for women with bone metastases from breast cancer. Clodronate (eight trials), pamidronate (six trials) or ibandronate (two trials) were compared to placebo or no-treatment control. A published meta-analysis of published data from six trials detected a reduction in the risk of skeletal events (excluding hypercalcemia) with bisphosphonates (relative risk of skeletal event, 0.88; 95% confidence interval, 0.81 to 0.96; p=0.004). Seven of nine double-blind trials and two of three open-label trials that assessed pain or analgesic use detected significantly reduced pain scores or analgesic use with bisphosphonates. Although five trials (four double-blind and one open-label) evaluated quality of life, there is no clear evidence of improvement with bisphosphonate therapy.

- Two randomized trials did not detect significant differences in skeletal events or pain between intravenous zoledronate and intravenous pamidronate in women with bone metastases from breast cancer.

- Three randomized trials evaluated the addition of oral bisphosphonates to chemotherapy or hormonal therapy for women with advanced breast cancer but no evidence of bone metastases. A published meta-analysis did not detect a significant difference in the risk of developing bone metastases (relative risk, 0.99; 95% confidence interval, 0.67 to 1.47) with bisphosphonates, compared to placebo or no treatment. Quality of life was measured in one trial, which did not detect a significant difference between pamidronate and control.

- A published meta-analysis of published data from nine trials did not detect a significant improvement in survival when bisphosphonates were administered to women with advanced breast cancer, with or without bone metastases (relative risk of death, 0.99; 95% confidence interval, 0.93 to 1.04).

- Three trials compared oral clodronate with placebo or no treatment as adjuvant therapy for early-stage breast cancer. They obtained conflicting results with respect to the effect of bisphosphonates on the development of bone metastases and survival.

- One randomized placebo-controlled trial detected an increased rate of gastrointestinal complaints with oral clodronate. Local reactions at the injection site were more common with pamidronate than with placebo, no-treatment control, or zoledronate. Uveitis is a rare but documented complication of treatment with pamidronate, requiring urgent referral to an ophthalmologist.

- The standard doses of the bisphosphonates reviewed here are: oral clodronate 1.6 g/day, intravenous pamidronate 90 mg every 3-4 weeks, and intravenous zoledronate 4 mg every 3-4 weeks. Randomized trials that compared different doses detected no significant differences in pain scores among doses, but observed that 3.2 g of clodronate was associated with hypocalcemia and that pain was reduced more quickly with 90 mg of pamidronate compared to lower doses.
Updated 2004 Key Evidence

- In the population randomized in one of the two pamidronate versus zoledronate trials, an unplanned multiple event analysis of patients with breast cancer who received zoledronate showed a significant reduction in the risk of developing skeletal complications compared with patients who received pamidronate (20% reduction; \( p=0.025 \)). A retrospective analysis restricted to breast cancer patients with at least one osteolytic metastasis showed a 10% reduction in skeletal-related events with zoledronate (\( p=0.058 \)). Further multiple-event analysis in this group showed a 30% proportionate reduction in the risk of developing skeletal complications in the zoledronate group (\( p=0.010 \)).

- Pooled data from three randomized trials comparing intravenous ibandronate to placebo and oral ibandronate to placebo were analyzed and published in abstract form. Skeletal-related events and bone pain were significantly reduced with both intravenous and oral ibandronate compared with placebo. Quality of life was improved with both intravenous and oral ibandronate.

Related Guidelines

- Practice Guideline #3-14: The Use of Bisphosphonates in Men with Hormone-Refractory Prostate Cancer (in development).

- Practice Guideline #6-4: The Role of Bisphosphonates in the Management of Skeletal Complications for Patients with Plasma Cell Myeloma (in development).

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The Practice Guidelines Initiative is sponsored by:

Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:

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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care (PEBC). The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.1 The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network, which is expected to consult with relevant stakeholders, including CCO.

Reference:
I. QUESTIONS

- Should bisphosphonates be used to reduce pain, reduce the likelihood of skeletal events other than hypercalcemia (i.e., fractures, requirement for radiation therapy, surgery), improve quality of life, or improve survival in women with bone metastases due to breast cancer?
- Should bisphosphonates be used to reduce the likelihood of bone metastases or improve survival in women with breast cancer that is locally advanced or metastatic to sites other than bone?
- Should bisphosphonates be used to reduce the risk of bone metastases or to improve survival in women with early-stage breast cancer?

II. CHOICE OF TOPIC AND RATIONALE

Bone metastases are common in advanced cancer. Certain tumor types, principally carcinomas of breast, lung and prostate, have a marked predilection for bone. These three sites together account for 80% of patients who have solid tumors metastatic to bone (1). Breast cancer typically results in mixed but predominantly lytic lesions in bone.

With breast cancer, bone is the first site of relapse in 47% of patients and the median survival of women with metastatic disease apparently confined to bone is two years (2). It was estimated that in 2001, 5500 women in Canada would die from breast cancer (3).

The destructive effects of metastases on bone are mediated by the local production of a variety of growth factors by the tumour cells, causing the excess action of osteoclasts which remove mineralized bone at a greater rate than it can be replaced. The bisphosphonates are a class of compounds that inhibit osteoclasts, which led to interest in their use as a supportive therapy to modify the morbidity of metastatic bone disease (4).

The use of bisphosphonates in patients with metastatic breast cancer has become part of standard practice. Since the literature review for the 1998 practice guideline, a substantial amount of new evidence has appeared, including new randomized trials, updates of previously identified randomized trials, practice guidelines and a meta-analysis. Although
most of these recent publications deal with patients who have metastatic breast cancer, there are now studies that address the benefits of using bisphosphonates on an adjuvant basis.

In view of the extensive amount of new data, a formal review of the guideline was carried out, as opposed to a simple update of the evidence, and the additional question of adjuvant use of bisphosphonates was formally included in the guideline report.

III. METHODS
Guideline Development
This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario’s Program in Evidence-based Care, using the methods of the Practice Guidelines Development Cycle (5). Evidence was selected and reviewed by one member of the PGI Breast Cancer DSG. Members of the DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the use of bisphosphonates in patients with breast cancer, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI editorially independent of Cancer Care Ontario, and the Ontario Ministry of Health and Long-term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Guideline History
This practice guideline report was originally completed in November 1998 and published in Current Oncology 1999;6(3):144-54. The 1998 guideline made the following recommendations:

- Women with breast cancer who have bone metastases should be offered treatment with oral clodronate or intravenous pamidronate. There is evidence from randomized controlled trials that once bone metastases are present, the use of these agents in addition to chemotherapy or hormones can significantly reduce skeletal events including bone pain and the need for radiation therapy.
- Intravenous clodronate has not been examined for its ability to reduce morbidity of bone metastases with long-term use. When clodronate is used for this purpose, the oral route is recommended.
- In patients with bone metastases and pain, either pamidronate or clodronate may be a useful adjunct to conventional measures for pain control.
- There is insufficient evidence to recommend treatment with bisphosphonates for women with breast cancer who do not have bone metastases, unless it is being prescribed for other indications such as osteoporosis.

Since 1998, the medical literature has been monitored for new evidence relevant to the guideline. In 2002, the Breast Cancer DSG felt that the original guideline document and the new evidence should be integrated. This guideline report reflects the evidence up to August 2002 and includes revised draft recommendations based on that evidence.
Original 2002 Literature Search Strategy
The MEDLINE database was searched from 1976 to August 2002 using disease-specific text words and subject headings (breast, mammary, cancer, carcinoma, neoplasm[s]), treatment-specific terms (diphosphonates, bisphosphonates, clodronate, pamidronate, etidronate, alendronate,ibandronate, zoledronate), and design-specific terms (meta-analysis, randomized controlled trial[s], practice guideline). The searches were not restricted by language. Issue 3 (2002) of the Cochrane Library, conference proceedings from the American Society of Clinical Oncology (ASCO) (1997-2002) and the San Antonio Breast Cancer Symposium (SABCS) (2001), and bibliographies were also searched. The Canadian Medical Association (CMA) Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp), the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) and other websites were searched for existing evidence-based practice guidelines.

Updated 2004 Literature Search Strategy
The original literature search was updated using MEDLINE (September 2002 to February 2004), the Cochrane Library (Issue 1, 2004), conference proceedings from the ASCO (2003) meeting and the SABCS (2002-2003), and bibliographies. Relevant websites were searched for new evidence-based practice guidelines.

Inclusion Criteria
Articles were eligible if they met all of the following criteria:
1. They were published reports, or abstracts from the ASCO or SABCS meetings.
2. They presented results of a meta-analysis or randomized controlled trial that compared:
   i. treatment with a bisphosphonate to observation or placebo;
   ii. two bisphosphonates;
   iii. two or more doses of the same bisphosphonate; or
   iv. the same bisphosphonate given by two routes of administration.
3. Trial participants were primarily patients with breast cancer (early-stage or advanced) although trial participants could also include patients with other solid tumours or myeloma.
4. Results were reported, by treatment group, for at least one of the following outcomes: survival, quality of life, and adverse effects. Additional outcomes of interest for patients with bone metastases from breast cancer included bone pain (measured using a pain scale or analgesic consumption) and skeletal events, other than hypercalcemia (as bisphosphonates are acknowledged to be an effective intervention for this complication). The development of bone metastases was also an outcome of interest in patients without bone metastases at the time of randomization.

Evidence-based practice guidelines and systematic reviews addressing the guideline questions were also included.

Synthesizing the Evidence
Because a well-conducted published meta-analysis was available (6), the Breast Cancer DSG did not conduct their own pooled analysis. The DSG did, however, conduct supplementary sensitivity analyses to make the meta-analysis more directly relevant to the guideline questions listed on page 1 of this report and to assess the impact of recently published evidence. For both the published meta-analyses and the sensitivity analyses by the DSG, the overall effect of bisphosphonates versus control was determined by pooling data using the Review Manager software (RevMan 4.1) provided by the Cochrane Collaboration (Metaview© Update Software). Results are expressed as relative risks (also known as risk ratios) with 95%
confidence intervals (CI). A relative risk (RR) >1.0 indicates that patients in the bisphosphonate group had a higher probability of experiencing an event compared with those in the control group; conversely, a relative risk <1.0 favours bisphosphonate over control. The published meta-analysis presented pooled results based on the fixed-effects model but noted that “random-effects models were also examined”. In order to facilitate direct comparisons with the results of the published meta-analysis, the DSG used the fixed-effects model for sensitivity analyses.

In the published meta-analysis, mortality data were pooled across a set of trials in patients with advanced breast cancer (6). In the first sensitivity analysis, the DSG restricted this analysis to patients with bone metastases. The second sensitivity analysis was restricted to patients without evidence of bone metastases. In the third sensitivity analysis, mortality data from a trial of adjuvant bisphosphonates that was published after completion of the published meta-analysis was added. In all cases, the numbers of patients dying during the trial and the numbers randomized were used for the meta-analysis.

IV. RESULTS
Original 2002 Literature Search Results
The literature search found the following articles and abstracts, which are summarized in this practice-guideline report:

- three evidence-based practice guidelines from other guideline-development groups that provide recommendations on the use of bisphosphonates in breast cancer (7-9);
- two relevant systematic reviews: one without meta-analysis, published in 1998 (10), and one with meta-analysis, published in 2001 (6);
- twenty-eight relevant randomized trials (11-38), nine of which (12,17,18,23,28,35-38) were not included in the most recent systematic review (6). Twenty-nine randomized trials were found by the literature search, but one cross-over trial of pamidronate versus placebo in ten patients was not included because of inadequate presentation of results (39);

Updated 2004 Search Results
- one update to an evidence-based practice guideline on the use of bisphosphonates in breast cancer (1u); and
- one full report (2u) of skeletal complication results from a randomized trial previously reported in abstract form only (25), three updates (3u-5u) to two randomized trial results included in the original guideline (27,34), and the results from a study, presented in two abstracts at the 2003 SABCS, which pooled data from three randomized trials to compare intravenous and oral ibandronate with placebo (6u,7u).

Evidence-based Guidelines
Original 2002 evidence summary
In 1998, the Scottish Intercollegiate Guidelines Network reviewed four randomized trials (15,19,21,24) and recommended that “Bisphosphonates should be considered in the management of metastatic bone disease.” (7).

A more recent guideline by ASCO reviewed five trials published up to 1999 (15,20,21,22,24) and recommended intravenous pamidronate for women with metastatic breast cancer who have lytic destruction of bone on plain radiographs or a computerized tomography (CT) scan, and who are receiving systemic hormonal therapy or chemotherapy (8). The guideline recommended that pamidronate should be continued until there is a “substantial” decline in performance status. The ASCO document also stated that current standards of care for cancer pain (i.e., analgesics and local radiation therapy) should not be
displaced by bisphosphonates. Intravenous pamidronate, used concurrently with systemic chemotherapy and/or hormonal therapy, was recommended to relieve pain caused by osteolytic metastases. The guideline did not recommend starting bisphosphonates in women without evidence of bony metastases, at any stage of disease, even in the presence of extraskeletal metastases.

The updated Canadian guideline on adjuvant systemic therapy for node-positive cancer, published in 2001 by the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer (9), included a review of three randomized trials of adjuvant clodronate (32-34). The guideline stated that "The routine use of bisphosphonates as adjuvant therapy is not recommended. Patients should be offered the opportunity to participate in clinical trials whenever possible."

The first two guidelines discussed above did not include trials published after 1999 and the Canadian guideline was restricted to the adjuvant use of bisphosphonates in early-stage disease. The Breast Cancer DSG reviewed these three practice guidelines and decided to update and revise its own practice guideline on bisphosphonates (40).

Updated 2004 evidence summary

An update to the ASCO practice guideline on the role of bisphosphonates in breast cancer was published in November 2003 (1u). Based predominately on evidence from a large randomized trial (27), the original recommendation for the treatment of lytic bone disease was expanded to include intravenous zoledronate in addition to pamidronate for women with metastatic breast cancer who show plain radiographs or a CT scan that show lytic destruction of bone and who are receiving systemic hormonal therapy of chemotherapy. The guideline also extended its recommendation for the role of bisphosphonates as pain control, stating that among other therapeutic options, intravenous pamidronate or zoledronate 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.

Systematic Reviews

The lead author of the original PGI guideline on bisphosphonates in breast cancer, DJ Bloomfield, published a systematic review in 1998 that covered the use of bisphosphonates in breast cancer, multiple myeloma and a range of other cancers (10). Bloomfield's review included the same evidence as the 1998 practice guideline by the Breast Cancer DSG and will not be discussed further here.

A systematic review and meta-analysis by Pavlakis and Stockler for the Cochrane Breast Cancer Group (6), last updated in November 2001, provided a summary of the evidence from 19 randomized trials of bisphosphonates in breast cancer (11,13-16,19-22,24-27,29-34). The review was based on a search of EMBASE, CANCERLIT, the Cochrane Breast Cancer Group's register of randomized trial reports, meeting proceedings, and bibliographies, but the time interval for the literature search was not specified. The objectives of the Cochrane review, "to assess the effect of bisphosphonates on skeletal events, bone pain, quality of life and survival in women with either early breast cancer or advanced breast cancer", closely match those for this guideline report. The Cochrane review included randomized trials comparing therapy for breast cancer that included a bisphosphonate to the same therapy without a bisphosphonate, as well as trials of one bisphosphonate versus another. Skeletal events (new bone metastases, pathologic fractures, spinal cord compression, irradiation or surgery on bone, development or progression of bone pain), overall survival, quality of life, hypercalcemia, adverse drug effects, and disease recurrence were the outcomes of interest for the Cochrane review. The Cochrane reviewers assessed trial reports for study quality using the MERGE criteria (41). The reviewers abstracted data for pooling from published reports and
abstracts, and contacted authors of included papers for additional evidence. Meta-analysis was conducted on an intention-to-treat basis using the fixed-effects model.

**Randomized Trials**

**Original 2002 evidence summary**

Thirty-three comparisons from 28 randomized trials are summarized in Table 1 (11-38). Five trial reports contributed to two comparisons (17,26,27,28,38). Five trials were reported only in abstract form (25,26,33,36,38).

Nineteen randomized trials of bisphosphonates in breast cancer (11,13-16,19-22,24-27,29-34) were included in the systematic review and meta-analysis by Pavlakis and Stockler for the Cochrane Breast Cancer Group (6). For this guideline report, skeletal event rates, median time to skeletal event, and median survival time were abstracted from the Cochrane review. Data on pathologic fracture rate, radiotherapy rate, pain score, analgesic use, quality of life, and adverse effects were abstracted from published trial reports.

Eight randomized trials were outside the scope of the Cochrane review noted above (6) but were included in this guideline report: five trials that evaluated the use of bisphosphonates for managing metastatic bone pain among patients with various types of cancer, including patients with breast cancer (12,17,18,23,28), and three trials of different doses of bisphosphonates (35-37).

Preliminary results of a randomized trial of oral ibandronate versus placebo, which were reported at the 2002 ASCO meeting after completion of the Cochrane review, were also reviewed for this guideline (38).

**Updated 2004 Evidence Summary**

Eligible articles identified in the updated literature search (2u-7u) were added to Table 1.

**Table 1.** Randomized trials eligible for inclusion in the practice guideline report on the use of bisphosphonates in women with breast cancer.

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<td></td>
</tr>
<tr>
<td></td>
<td>iv clodronate vs. placebo</td>
<td>2</td>
<td>11,12</td>
</tr>
<tr>
<td></td>
<td>oral clodronate vs. placebo</td>
<td>5</td>
<td>13,15-18</td>
</tr>
<tr>
<td></td>
<td>vs. observation</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>iv pamidronate vs. placebo</td>
<td>4</td>
<td>19-21,23</td>
</tr>
<tr>
<td></td>
<td>vs. observation</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>oral pamidronate vs. observation</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>iv ibandronate vs. placebo</td>
<td>2</td>
<td>25,2u,6u,7u</td>
</tr>
<tr>
<td></td>
<td>oral ibandronate vs. placebo</td>
<td>2</td>
<td>38,6u,7u</td>
</tr>
<tr>
<td>3 RCTs comparing different bisphosphonates</td>
<td>iv clodronate vs. iv pamidronate</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>iv zoledronate vs. iv pamidronate</td>
<td>2</td>
<td>27,3u,4u,28</td>
</tr>
<tr>
<td>1 RCT comparing routes of administration</td>
<td>oral clodronate vs. iv clodronate</td>
<td>1</td>
<td>26*</td>
</tr>
</tbody>
</table>
Outcomes in Women with Bone Metastases from Breast Cancer

Original 2002 Evidence Summary

Evidence is available from 19 randomized trials of bisphosphonates (clodronate, pamidronate or ibandronate), added to systemic chemotherapy or hormonal therapy, in women with advanced breast cancer and clinically evident bone metastases (11-28,38). These trials are listed in Table 2 (References 35-37 in Table 1 did not include a placebo or observation group. They are omitted from Table 2, but are discussed below under Dose and Route of Administration). Supplementary information was obtained from earlier reports for the Theriault, Hortobagyi, van Holten-Verzantvoort, Elomaa and Coleman trials (42-46). Eleven trials evaluated the impact of treatment with oral or intravenous bisphosphonates, given for one to three years, on a variety of skeletal events related to bone metastases (13-16,19-22,24-25,38) and five evaluated short-term treatment with oral or intravenous bisphosphonates for pain control (11,12,17,18,23). Three trials compared one bisphosphonate with another (26-28).

Thirteen of 16 trials of a bisphosphonate versus no bisphosphonate were placebo-controlled (11-13,15-21,23,25,38), the trial of clodronate versus pamidronate was open (26), and both trials of zoledronate versus pamidronate were double-blind (27,28). The Cochrane reviewers rated two of the twelve trials included in their review as low-quality (6). Because the trial by Martoni et al had inadequate blinding and monitoring of outcomes, and a relatively high withdrawal rate, its results were judged by the Cochrane reviewers to be at moderate to high risk of bias (11). In this trial, patients were randomized to seven days of treatment with intravenous clodronate or placebo, and pain was assessed on days 0, 3, and 7. After seven days, patients entered an open phase of the trial that compared rates of pathologic fractures during two months of treatment with intramuscular clodronate or observation. The Cochrane reviewers' concerns about bias applied to the second part of the trial, and only data from the first seven days were included in the Cochrane review and in this practice guideline report. The trial by Elomaa et al (16) was also given a poor rating by the Cochrane reviewers because of unclear concealment of allocation. The quality rating assigned to the latter study indicated that the trial results are likely to be biased, and a sensitivity analysis was conducted by the Cochrane reviewers to investigate the impact of this trial on their pooled analysis (6).

Updated 2004 Evidence Summary

Table 2 was updated to include the references for the two updates to the Rosen et al trial and the full publication of the Body et al trial.
Table 2. Randomized trials of bisphosphonates in women with bone metastases from breast cancer.

<table>
<thead>
<tr>
<th>1st author, year (reference)</th>
<th># patients randomized (# evaluable)</th>
<th>Treatment groups</th>
<th>Route, dose &amp; frequency</th>
<th>Planned duration of treatment</th>
<th>Included in Cochrane review</th>
<th>Outcomes counted as a 'skeletal event' by the investigators and included in the Cochrane meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clodronate vs. placebo/observation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martoni, 1991 (11)</td>
<td>38 (33)</td>
<td>clodronate</td>
<td>intravenous 300 mg daily</td>
<td>7 days</td>
<td>yes</td>
<td>not included in Cochrane meta-analysis of skeletal events</td>
</tr>
<tr>
<td>Ernst, 1992 (12)</td>
<td>24 (21)</td>
<td>clodronate</td>
<td>intravenous 600 mg</td>
<td>single dose (1 week cross-over)</td>
<td>no</td>
<td>trial not eligible for Cochrane review</td>
</tr>
<tr>
<td>Tubiana-Hulin, 2001 (13)</td>
<td>144 (137)</td>
<td>clodronate</td>
<td>oral 1.6 g daily</td>
<td>12 months</td>
<td>yes</td>
<td>hypercalcemia, new bone metastases, new or increased bone pain, radiotherapy to bone, pathologic fracture, death due to bone metastases</td>
</tr>
<tr>
<td>Kristensen, 1999 (14)</td>
<td>100 (99)</td>
<td>clodronate</td>
<td>oral 400 mg b.i.d.</td>
<td>2 years</td>
<td>yes</td>
<td>- hypercalcemia, - radiotherapy to bone, - pathologic fracture</td>
</tr>
<tr>
<td>Paterson, 1993 (15)</td>
<td>173 (173)</td>
<td>clodronate</td>
<td>oral 1.6 g daily</td>
<td>3 years</td>
<td>yes</td>
<td>- hypercalcemia, - radiotherapy to bone, - pathologic fracture</td>
</tr>
<tr>
<td>Elomaa 1988 (16)</td>
<td>34 (34)</td>
<td>clodronate</td>
<td>oral 1.6 g daily</td>
<td>12 months</td>
<td>yes</td>
<td>not included in Cochrane meta-analysis of skeletal events</td>
</tr>
<tr>
<td>O'Rourke, 1995 (17)</td>
<td>84 (80)</td>
<td>clodronate</td>
<td>oral 0.4, 1.6 or 3.2 g daily</td>
<td>4 weeks</td>
<td>no</td>
<td>trial not eligible for Cochrane review</td>
</tr>
<tr>
<td>Robertson, 1995 (18)</td>
<td>55 (55)</td>
<td>clodronate</td>
<td>oral 1.6 g daily</td>
<td>until end of study (median = 56 days)</td>
<td>no</td>
<td>trial not eligible for Cochrane review</td>
</tr>
<tr>
<td><strong>Pamidronate vs. placebo/observation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hultborn, 1999 (19)</td>
<td>404 (404)</td>
<td>pamidronate</td>
<td>intravenous 60 mg over 1 hour 3-4 weekly</td>
<td>2 years</td>
<td>yes</td>
<td>- hypercalcemia, - increased bone pain, - pathologic fracture, - paresis</td>
</tr>
<tr>
<td>Theriault, 1999 (20)</td>
<td>372 (371)</td>
<td>pamidronate</td>
<td>intravenous 90 mg over 2 hours 3-4 weekly</td>
<td>2 years (pooled with Hortobagyi trial)</td>
<td>yes</td>
<td>- hypercalcemia, - pathologic fracture, - radiotherapy to bone, - surgical intervention, - spinal cord compression</td>
</tr>
</tbody>
</table>
Table 2. Randomized trials of bisphosphonates in women with bone metastases from breast cancer.

<table>
<thead>
<tr>
<th>1st author, year (reference)</th>
<th># patients randomized (# evaluable)</th>
<th>Treatment groups</th>
<th>Route, dose &amp; frequency</th>
<th>Planned duration of treatment</th>
<th>Included in Cochrane review</th>
<th>Outcomes counted as a 'skeletal event' by the investigators and included in the Cochrane meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hortobagyi, 1998 (21)</td>
<td>382 (380)</td>
<td>pamidronate</td>
<td>intravenous 90 mg over 2 hours 3-4 weekly</td>
<td>24 cycles</td>
<td>yes (pooled with Theriault trial)</td>
<td>hypercalcemia, pathologic fracture, radiotherapy to bone, surgical intervention, spinal cord compression</td>
</tr>
<tr>
<td>Conte, 1996 (22)</td>
<td>295 (283)</td>
<td>pamidronate</td>
<td>intravenous 45 mg over 1 hour 3 weekly</td>
<td>until progressive bone disease</td>
<td>yes</td>
<td>hypercalcemia, pathologic fracture, radiotherapy to bone, surgical intervention</td>
</tr>
<tr>
<td>Coleman, 1997 (23)</td>
<td>52 (47)</td>
<td>pamidronate</td>
<td>intravenous 120 mg over 2 hours</td>
<td>single dose</td>
<td>no</td>
<td>trial not eligible for Cochrane review</td>
</tr>
<tr>
<td>van Holten-Verzantvoort, 1993 (24)</td>
<td>173 (161)</td>
<td>pamidronate</td>
<td>oral 300 mg daily</td>
<td>until end of study</td>
<td>yes</td>
<td>hypercalcemia, changes to medications, radiotherapy to bone, surgical intervention, death, toxicity</td>
</tr>
</tbody>
</table>

Ibandronate vs. placebo/observation

<table>
<thead>
<tr>
<th>Body, 1999 (25) [abstract]</th>
<th>Body, 2003 (2u)</th>
<th>ibandronate placebo</th>
<th>intravenous 2 mg 4 weekly</th>
<th>2 years</th>
<th>yes</th>
<th>not included in Cochrane meta-analysis of skeletal events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tripathy 2002 (38) [abstract]</td>
<td></td>
<td>ibandronate placebo</td>
<td>oral 20 or 50 mg daily</td>
<td>not reported</td>
<td>no</td>
<td>published after Cochrane review</td>
</tr>
</tbody>
</table>

Comparison of two bisphosphonates

<table>
<thead>
<tr>
<th>Diel, 1999 (26) [abstract]</th>
<th>361 (318)</th>
<th>clodronate 2.4 g/day oral 900 mg iv 60 mg iv iv 3-4 weekly</th>
<th>2 years</th>
<th>yes</th>
<th>not included in Cochrane meta-analysis of skeletal events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosen, 2001 (27,3u,4u)</td>
<td>1648 (1640) 1130 with breast cancer*</td>
<td>zoledronate intravenous 4 or 8 mg 90 mg 3-4 weekly</td>
<td>12 months</td>
<td>yes</td>
<td>not included in Cochrane meta-analysis of skeletal events</td>
</tr>
<tr>
<td>Berenson, 2001 (28)</td>
<td>280 (280) 172 with breast cancer*</td>
<td>zoledronate intravenous 0.4, 2 or 4 mg 90 mg 4 weekly</td>
<td>10 months</td>
<td>no</td>
<td>trial not eligible for Cochrane review</td>
</tr>
</tbody>
</table>

* Also included patients with other cancers; iv, intravenous
**Bisphosphonate versus no Bisphosphonate**

**Skeletal events**

Original 2002 evidence summary

The number of skeletal events observed over the treatment period was reported for nine randomized trials of bisphosphonate versus no bisphosphonate in women with bone metastases from breast cancer (Table 3). Eight trials reported a composite outcome, based on number of skeletal events, but there was variation from study to study in the types of events included (Table 2). For seven trials, skeletal-event rate or time to first skeletal event was identified by investigators as the primary outcome (13-15,19-21,27). A significant difference between bisphosphonates and control in the incidence of skeletal events was reported for three trials (20,21,24). In the two largest trials of pamidronate, differences between the pamidronate and control groups began to emerge after approximately six months (20,21).

The skeletal-event data presented in Table 3 reflect those used for the Cochrane meta-analysis (6). In some cases, these data were obtained directly from investigators by the Cochrane review group and differ slightly from those in the published reports. Pooled data from Protocols 18 and 19 by the Aredia Breast Cancer Study Group, also reported separately by Theriault et al (20) and Hortobagyi et al (21), were used for the meta-analysis (41). The Cochrane reviewers planned to exclude hypercalcemia from their definition of skeletal events, but data on the composite outcome of skeletal events excluding hypercalcemia were not available for all trials. For this reason, the reviewers performed two pooled analyses, one with and one without hypercalcemia.

The Cochrane meta-analysis of data from six trials (13,14,19-21,24) detected a significant reduction in the overall risk of experiencing a skeletal event (excluding hypercalcemia) with bisphosphonate treatment in women with bone metastases from breast cancer (relative risk of a skeletal event [RR], 0.88; 95% confidence interval [CI], 0.81 to 0.96; p=0.004). A somewhat larger effect was observed when hypercalcemia was included as a skeletal event for eight trials (13-15,19-22,24) (RR, 0.86; 95% CI, 0.80 to 0.91; p<0.00001).

In addition to the composite outcome, all nine trials summarized in Table 3 reported some data on pathologic fractures. It was not possible to ascertain overall fracture rates for four trials (15,21,22,27), because they reported vertebral and non-vertebral fractures separately, or reported only events/patient-year. Radiotherapy to bone for pain was another commonly reported outcome in these trials (Table 3).

Only limited data were available from the randomized trial of oral ibandronate versus placebo by Tripathy et al (38). The abstract reported statistically significant differences in the need for radiotherapy between placebo and ibandronate (at either the 20 mg or 50 mg dose) but gave no detailed results.

Updated 2004 evidence summary

In their full report on skeletal complications, Body et al reported the skeletal morbidity period rate in women randomized to ibandronate (6mg), ibandronate (2mg), or placebo (2u). At 96 weeks of follow-up, the median time from treatment randomization to a new bone event was significantly longer for patients receiving 6mg of ibandronate compared with patients receiving the placebo (50.6 weeks versus [vs.] 33.1 weeks; p=0.018). Median time to first new bone event for women receiving 2mg ibandronate was not significantly different from either the 6mg group or the placebo group (44.6 weeks).

The pooled results from three randomized trials were reported at the 2003 SABSC (6u,7u). Women with metastatic breast cancer receiving intravenous or oral ibandronate experienced significant reductions in the risk of skeletal-related events compared with placebo (risk reduction with intravenous and oral ibandronate, respectively (risk reduction...
with intravenous administration: 40%; p=0.0033; risk reduction with oral administration: 38%; p<0.0001) (6u).

**Bone pain**

Original 2002 evidence summary

The effect of bisphosphonates on pain from bone metastases was assessed in thirteen randomized trials (11-14,17-25). Changes from baseline in pain scores and analgesic use for twelve trials of clodronate or pamidronate are summarized in Table 4 (11-14,17-24). All but three of these trials (14,22,24) were double-blind. In an abstract for the 1999 ASCO meeting, Body et al reported a “significant improvement in bone pain score (p=0.0006)” with intravenous ibandronate compared to placebo, but no details were given (25).

Updated 2004 evidence summary

Body et al (25) published their full report in 2003 (2u). At 96 weeks of follow-up, bone pain was significantly improved in women receiving 6mg ibandronate compared to those receiving placebo and those receiving only 2mg ibandronate.

Based on the data collected in three randomized trials, treatment with intravenous or oral ibandronate produced a rapid initial reduction in bone pain that was maintained below baseline pain levels over two years (7u). The mean change from baseline was -0.28 with intravenous ibandronate versus +0.21 with placebo (p<0.001) and -0.10 with oral ibandronate versus +0.20 with placebo (p=0.001). Analgesic use scores were also improved with both intravenous (p=0.08) and oral (p=0.019) ibandronate. These results are summarized in Table 4.

**Quality of life**

Original 2002 evidence summary

Five randomized trials measured quality of life during treatment with bisphosphonates (given in addition to chemotherapy or endocrine therapy) for breast cancer with bone metastases (14,20,21,24,25). Four of the trials were double-blind (20,21,24,25). There were two trials of oral (14,24) and three of intravenous bisphosphonates (20,21,25).

An open-label trial of oral clodronate versus no bisphosphonate, by Kristensen et al, detected no significant differences between treatment groups in change from baseline on EORTC-C30 or HADS scores over six months of treatment (14). Van Holten-Verzantvoort et al designed a 17-item questionnaire to measure quality of life (mobility impairment, bone pain, toxicity, and fatigue) in their randomized trial of oral pamidronate versus placebo (24). Pain results are described in Table 4. Mobility was significantly improved with pamidronate, compared to placebo (p=0.03), but there were no differences on the toxicity and fatigue scales.

Theriault et al noted that quality of life, measured by the Spitzer index, declined with both intravenous pamidronate and placebo, but there was no significant difference between groups (20). In a trial of similar design, Hortobagyi et al stated that fewer patients on intravenous pamidronate had decreases in Spitzer quality-of-life scores, compared to placebo, but these differences were not statistically significant (21). Data from these two trials was pooled and reported by Lipton et al (42), who detected less worsening of quality of life from baseline with pamidronate compared to placebo, but the difference between groups was not significant (p=0.088).

---

1 European Organization for the Research and Treatment of Cancer
2 Hospital Anxiety and Depression Scale
An abstract by Body et al described a significant improvement in EORTC Quality of Life Questionnaire (QLQ)-30 scores with intravenous ibandronate, compared to placebo, but reported no details (25).

**Updated 2004 evidence summary**

Pooled data collected in three randomized trials showed improved EORTC QLQ-30 scores for both intravenous (p=0.004) and oral ibandronate (p=0.03) when compared with placebo (6u). No further details were provided.

**Survival**

Survival data were available from eight randomized trials of a bisphosphonate versus no bisphosphonate in women with bone metastases from breast cancer (Table 5). Only the trial by Elomaa et al detected a significant difference between treatments (16). This trial included only 34 patients, and was designed to study the ability of clodronate to inhibit tumour-induced bone resorption and to prevent hypercalcaemia (45).

The Cochrane reviewers (6) pooled survival data from six of these trials (14,16,20,21,22,24), along with data from three trials in women with advanced breast cancer but no evidence of bone metastases (29-31). The pooled mortality risk ratio for these nine trials was 0.99 (95% CI, 0.93 to 1.04). Because of concerns about the quality of the Elomaa trial (16), the Cochrane reviewers repeated the meta-analysis without this trial, and obtained a risk ratio of 1.00 (95% CI, 0.94 to 1.05). Survival data from the trial by Hultborn et al (19) and the 1993 trial by van Holten-Verzantvoort et al (24) were included in the Cochrane review tables but not in their meta-analysis. Survival curves were not presented in published reports of these two trials. Hultborn et al reported median survival but did not report the number of deaths in their study (19). Van Holten-Verzantvoort et al reported 48 deaths in the pamidronate group (n=81) and 61 in the control group (n=80), data that do not seem to be consistent with a reported p-value of 0.98 for median survival (24).

The developers of this guideline repeated the meta-analysis with only the six trials involving patients with bone metastases and obtained a mortality risk ratio of 1.0 (95% CI, 0.95 to 1.06).
Table 3. Skeletal events - randomized trials of bisphosphonates vs. placebo/observation in women with bone metastases from breast cancer.

<table>
<thead>
<tr>
<th>1st author, year (reference)</th>
<th>Treatment groups</th>
<th>Skeletal event as defined by the trial investigators*, with hypercalcemia (% patients)</th>
<th>Skeletal event as defined by the trial investigators*, without hypercalcemia (% patients)</th>
<th>Median time to first skeletal event in months (log-rank p-value)*</th>
<th>Pathologic fractures** (% patients)</th>
<th>Radiotherapy to bone** (% patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clodronate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubiana-Hulin, 2001 (13)</td>
<td>oral clodronate placebo</td>
<td>61%</td>
<td>70%</td>
<td>8.7 (p=0.05)</td>
<td>12%</td>
<td>not reported</td>
</tr>
<tr>
<td>Kristensen, 1999 (14)</td>
<td>oral clodronate placebo</td>
<td>29%</td>
<td>22%</td>
<td>22.5** (p=0.015)</td>
<td>6%</td>
<td>16%</td>
</tr>
<tr>
<td>Paterson, 1993 (15)</td>
<td>oral clodronate placebo</td>
<td>61%</td>
<td>not reported</td>
<td>9.9 (p=0.022)</td>
<td>6%</td>
<td>38%</td>
</tr>
<tr>
<td>Elomaa, 1988 (16,45)</td>
<td>oral clodronate placebo</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
<td>6%***</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Pamidronate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hultborn, 1999 (19)</td>
<td>iv pamidronate placebo</td>
<td>78%</td>
<td>61%</td>
<td>11.8 (p=0.006)</td>
<td>15%</td>
<td>27%</td>
</tr>
<tr>
<td>Theriault, 1999 (20)</td>
<td>iv pamidronate placebo</td>
<td>53%</td>
<td>51%</td>
<td>12.7** (p=0.001)</td>
<td>45%</td>
<td>31%</td>
</tr>
<tr>
<td>Hortobagyi, 1998 (21)</td>
<td>iv pamidronate placebo</td>
<td>50%</td>
<td>64%</td>
<td>not reached**</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Conte, 1996 (22)</td>
<td>iv pamidronate placebo</td>
<td>not reported</td>
<td>not reported</td>
<td>8.9 (p=0.02)</td>
<td>not reported</td>
<td></td>
</tr>
<tr>
<td>van Holten-Verzantvoort, 1993 (24)</td>
<td>oral pamidronate observation</td>
<td>64%</td>
<td>59%</td>
<td>14 (p=0.10)</td>
<td>7%</td>
<td>27%</td>
</tr>
</tbody>
</table>

* data from Cochrane review and meta-analysis, see last column of Table 2 for list of individual outcomes included in the composite outcome
** data from published reports of individual trials
*** during 12-month treatment period
+ pooled data
Table 4. Pain relief - randomized trials of bisphosphonates in women with bone metastases from breast cancer.

<table>
<thead>
<tr>
<th>1st author, year (reference)</th>
<th>Measurement tool</th>
<th>Assessed by</th>
<th>Assessment interval</th>
<th>Treatment groups</th>
<th>Pain score (change from baseline)*</th>
<th>Analgesic use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clodronate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martoni, 1991 (11)</td>
<td>10-cm visual analogue scale</td>
<td>patient</td>
<td>7 days</td>
<td>iv clodronate placebo</td>
<td>no significant difference between groups</td>
<td>% with decreased analgesic use: 27% (p=0.02)</td>
</tr>
<tr>
<td>Ernst, 1992 (12)</td>
<td>10-cm visual analogue scale</td>
<td>patient</td>
<td>7 days</td>
<td>iv clodronate placebo</td>
<td>difference between groups = -0.89 (p=0.004 in favour of clodronate)</td>
<td>no significant difference between groups</td>
</tr>
<tr>
<td>Tubiana-Hulin, 2001 (13)</td>
<td>visual analogue scale</td>
<td>patient</td>
<td>12 months</td>
<td>oral clodronate placebo</td>
<td>-11.8 (p&lt;0.01) + 4.5</td>
<td>% of patients taking analgesics: 67% (p=0.02) 84%</td>
</tr>
<tr>
<td>Kristensen, 1999 (14)</td>
<td>4-point scale</td>
<td>physician</td>
<td>18 months</td>
<td>oral clodronate placebo</td>
<td>no significant difference between groups</td>
<td>no significant difference in slopes when use plotted over 18 months</td>
</tr>
<tr>
<td>O'Rourke, 1995 (17)</td>
<td>10-cm visual analogue scale</td>
<td>patient</td>
<td>4 weeks</td>
<td>oral clodronate placebo</td>
<td>no significant difference between groups</td>
<td>no significant difference between groups</td>
</tr>
<tr>
<td>Robertson, 1995 (18)</td>
<td>10-cm visual analogue scale</td>
<td>patient</td>
<td>2 months</td>
<td>oral clodronate placebo</td>
<td>-0.9 (p=0.03) +0.4</td>
<td>no significant difference between groups</td>
</tr>
<tr>
<td><strong>Pamidronate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hultborn, 1999 (19)</td>
<td>10-cm visual analogue scale</td>
<td>patient</td>
<td>24 months</td>
<td>iv pamidronate placebo</td>
<td>&quot;significantly increased time to progression of pain&quot; with pamidronate (p=0.006) but data not reported</td>
<td>no significant difference between groups</td>
</tr>
<tr>
<td>Theriault, 1999 (20)</td>
<td>product of 4-point scales for severity &amp; frequency</td>
<td>patient</td>
<td>12 months</td>
<td>iv pamidronate placebo</td>
<td>+0.5 (p=0.007) +1.6</td>
<td>increase from baseline larger in the placebo group compared with pamidronate (p=0.001)</td>
</tr>
<tr>
<td>Hortobagyi, 1998 (21)</td>
<td>product of 4-point scales for severity &amp; frequency</td>
<td>patient</td>
<td>24 months</td>
<td>iv pamidronate placebo</td>
<td>more patients on placebo had increased pain than on pamidronate (p=0.015)</td>
<td>% with increased analgesic use: 26% (p=0.011) 40%</td>
</tr>
<tr>
<td>Conte, 1996 (22)</td>
<td>6-point scale</td>
<td>patient</td>
<td>not reported</td>
<td>iv pamidronate observation</td>
<td>marked improvement (2-point decrease): 44% (p=0.025) 30%</td>
<td>no significant difference between groups</td>
</tr>
<tr>
<td>Coleman, 1997 (23)</td>
<td>3-part score</td>
<td>patient</td>
<td>4 weeks</td>
<td>iv pamidronate placebo</td>
<td>≥20% reduction in combined pain, analgesic &amp; performance status score: 24% (p=0.1) 4%</td>
<td>no significant difference between groups</td>
</tr>
<tr>
<td>van Holten-Verzantvoort, 1993 (24,44)</td>
<td>3 items, 4-point scale</td>
<td>patient</td>
<td>24 months</td>
<td>oral pamidronate observation</td>
<td>more rapid increase in control group compared to pamidronate (p=0.02)</td>
<td>not reported</td>
</tr>
<tr>
<td><strong>Ibandronate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tripathy, 2003 (7u)</td>
<td>5-point scale</td>
<td>not reported</td>
<td>24 months</td>
<td>iv ibandronate placebo oral ibandronate placebo</td>
<td>-0.28 (p=0.001) +0.21 -0.10 (p=0.001) +0.20</td>
<td>improved score (p=0.08) improved score (p=0.019)</td>
</tr>
</tbody>
</table>

* positive number indicates increased pain and negative number indicates decreased pain, compared to baseline assessment
Table 5. Survival - randomized trials of bisphosphonates in women with bone metastases from breast cancer.

<table>
<thead>
<tr>
<th>1st author, year (reference)</th>
<th>Median follow-up (months)</th>
<th>Treatment groups</th>
<th>Median survival (months)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kristensen, 1999 (14)</td>
<td>not reported</td>
<td>oral clodronate</td>
<td>18.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>observation</td>
<td>18.0</td>
</tr>
<tr>
<td>Elomaa, 1988 (16)</td>
<td>&gt;12</td>
<td>oral clodronate</td>
<td>25 (p=0.004)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>placebo</td>
<td>14</td>
</tr>
<tr>
<td>Hultborn, 1999 (19)</td>
<td>12</td>
<td>iv pamidronate</td>
<td>18.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>placebo</td>
<td>18.3</td>
</tr>
<tr>
<td>Theriault, 1999 (20)</td>
<td>37</td>
<td>iv pamidronate</td>
<td>23.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>placebo</td>
<td>23.5</td>
</tr>
<tr>
<td>Hortobagyi, 1998 (21)</td>
<td>12</td>
<td>iv pamidronate</td>
<td>14.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>placebo</td>
<td>14.0</td>
</tr>
<tr>
<td>Conte, 1996 (22)</td>
<td>not reported</td>
<td>iv pamidronate</td>
<td>19.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>observation</td>
<td>21.0</td>
</tr>
<tr>
<td>van Holten-Verzantvoort, 1993 (24)</td>
<td>20</td>
<td>oral pamidronate</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>observation</td>
<td>24</td>
</tr>
<tr>
<td>Body, 1999 (25,2u)</td>
<td>not reported</td>
<td>iv ibandronate</td>
<td>27.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>placebo</td>
<td>26.5</td>
</tr>
</tbody>
</table>

* except for Theriault and Hortobagyi trials, data abstracted from Cochrane review (6)

**Clodronate versus Pamidronate**

An abstract by Diel et al for the 1999 ASCO meeting presented preliminary results from a randomized trial of oral clodronate versus intravenous clodronate versus intravenous pamidronate in women with bone metastases from breast cancer (26). It is not clear from the abstract if any blinding was employed. Vertebral fractures were observed in 10% of patients on oral clodronate, 18% on intravenous clodronate and 16% on pamidronate. Pain reduction was 15% with oral clodronate, 25% with intravenous clodronate and 30% with pamidronate, but assessment methods were not described, and it is not clear if these reductions refer to patients or scores.

**Zoledronate versus Pamidronate**

Original 2002 evidence summary

Two double-blind randomized trials have compared intravenous zoledronate (4 or 8 mg) to intravenous pamidronate 90 mg (27,28). Zoledronate was infused over 15 minutes in the Rosen trial and over 5 minutes in the Berenson trial, in contrast with pamidronate which was given over two hours. Both were administered every three to four weeks. The trial by Rosen et al randomized 1,130 women with skeletal metastases from breast cancer to 12 months of treatment with pamidronate or one of two doses of zoledronate (4 mg and 8 mg) (27). Very similar skeletal event rates (pathologic fracture, spinal cord compression, or radiotherapy to bone), time to first skeletal event, and pain scores were observed for pamidronate and zoledronate. Berenson et al compared three doses of zoledronate (0.4 mg, 2 mg, and 4 mg, given every four weeks for up to ten months) to pamidronate in patients with either breast cancer (n=172) or multiple myeloma (n=108) (28). They detected no significant differences between pamidronate and zoledronate in the proportions of patients receiving radiation therapy to bone (the primary outcome for this trial), skeletal events as a composite outcome (pathologic fracture, spinal cord compression, surgery to bone, radiotherapy to bone, or hypercalcemia), pathologic-fracture rate, or pain score.
Updated 2004 evidence summary

Two further papers, based on the population randomized in the study by Rosen et al (27), have been published. One reported longer-term follow-up results (3u), and the other reported a subgroup analysis confined to breast cancer patients with at least one lytic metastasis (4u). In the first, there was no statistically significant difference in the proportion of patients with at least one skeletal event at 25 months of follow-up (3u). No information was provided about pain scores. In the second, an unplanned multiple event analysis confined to patients with breast cancer showed a 20% proportionate reduction in the risk of developing skeletal complications for patients receiving zoledronate (p=0.025) (4u). A retrospective analysis of the subgroup of patients with breast cancer who had at least one osteolytic metastases reported an absolute 10% reduction in the skeletal event rate that was not statistically significant (p=0.058). A multiple event rate analysis in this subgroup showed a 30% proportionate reduction in the risk of developing skeletal complications in the zoledronate group (p=0.010). Results of pain scores in that subgroup were not reported.

Outcomes in Women with Locally Advanced or Extraskeletal Disease

Three randomized trials of oral bisphosphonates in women with advanced breast cancer (stage III or IV) but without clinically evident bone metastases are listed in Table 6 (29-31). Most trial participants also received chemotherapy or endocrine therapy. All three trials were included in the Cochrane review (6).

Two of three trials were placebo-controlled (29,30). All three studies were designed to evaluate the use of bisphosphonates over two years or more, but two trials suffered from high drop-out rates. In the trial by van Holten-Verzantvoort et al (31), 19 of 65 patients in the pamidronate group withdrew because of gastrointestinal complaints, resulting in an imbalance in the groups for long-term follow-up. Ten of 73 participants in the trial by Mardiak et al (29) were followed for less than two months (seven randomized to clodronate and three to placebo).

The percentage of women with extraskeletal metastases at study entry varied among the studies: 10% in the Mardiak trial (29), 100% in the Kanis trial (30), and 73% in the van Holten-Verzantvoort trial (31).

Bone Metastases

None of the individual trials detected a significant effect of treatment with a bisphosphonate on the incidence or time to development of bone metastases (29-31). Even with the increased power that results from pooling data from these trials, there was no significant advantage for bisphosphonates. Meta-analysis of incidence data by the Cochrane reviewers (6) did not detect any significant difference between bisphosphonates and control (RR for bone metastasis, 0.99; 95% CI, 0.67 to 1.47). Median time to the first detection of bone metastases was reported only for the Mardiak trial (13.4 months for clodronate and 28.4 months for placebo, p=0.43) (29).
Table 6. Randomized trials of bisphosphonates in women with advanced breast cancer but without evidence of bone metastases.

<table>
<thead>
<tr>
<th>1st author, year (reference)</th>
<th># patients randomized (# evaluable)</th>
<th>Treatment groups</th>
<th>Median follow-up (months)</th>
<th>Radiological evidence of bone metastasis* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mardiak, 2000 (29)</td>
<td>73 (63)</td>
<td>oral clodronate, 1.6 g/day placebo</td>
<td>84</td>
<td>30% 21%</td>
</tr>
<tr>
<td>Kanis, 1996 (30)</td>
<td>133 (133)</td>
<td>oral clodronate, 1.6 g/day placebo</td>
<td>not reported</td>
<td>23% 28%</td>
</tr>
<tr>
<td>van Holten-Verzantvoort, 1996 (31)</td>
<td>124 (124)</td>
<td>oral pamidronate, 300 mg/day observation</td>
<td>19 34</td>
<td>22% 20%</td>
</tr>
</tbody>
</table>

* data from Cochrane review and meta-analysis (6)

**Survival**

None of the trials listed in Table 6 detected a significant survival difference between bisphosphonates and control (29-31). In the trial by Mardiak et al (29), median overall survival was 59.4 months with clodronate and 54.7 months with placebo. After three years of follow-up, 40% of patients allocated to clodronate and 36% of those allocated to placebo had died in the trial by Kanis et al (30). At three years, 42% on pamidronate and 45% in the control group had died in the trial by van Holten-Verzantvoort et al (31).

The Cochrane reviewers included survival data from these three trials in their pooled analysis, along with data from six trials in women with bone metastases from breast cancer (6). As reported on page 10 of this guideline report, the pooled mortality risk ratio for these nine trials was 0.99 (95% CI, 0.93 to 1.04). Risk ratios for individual trials in patients with advanced breast cancer but no bone metastases were 0.82 (95% CI, 0.53 to 1.30) (29), 0.94 (95% CI, 0.73 to 1.23) (30), and 0.91 (95% CI, 0.61 to 1.35) (31), where a risk ratio <1.0 favours bisphosphonate treatment. The developers of this guideline repeated the meta-analysis with only the three trials involving patients without bone metastases and obtained a mortality risk ratio of 0.91 (95% CI, 0.74 to 1.11).

**Quality of Life**

Seventy-three percent of participants in the open-label trial by van Holten-Verzantvoort et al completed a 17-item quality of life questionnaire (31). There were no significant differences between the pamidronate and control groups in changes from baseline on scores for mobility impairment, gastrointestinal toxicity, bone pain, or fatigue.

**Outcomes in Women with Early-stage Breast Cancer**

Three randomized trials of bisphosphonates as part of adjuvant therapy following surgery in women with early-stage (stage I or II) breast cancer are listed in Table 7 (32-34). Treatment with bisphosphonates was planned for two (33,34) or three years (32). The trial by Diel et al was described in a full report in 1998 (47) and updated results were reported in an ASCO abstract in 2000 (33). All three trials were included in the Cochrane review (6). Only the trial by Powles et al was double-blind (34). There were some differences among the eligibility criteria for these trials. Participants in the Diel trial had T1-T4, N0-N2 disease with tumour...
cells detected in bone marrow aspirate (33,45). Those in the Saarto trial had node-positive disease (32).

**Bone Metastases**

The trial by Diel et al detected significant differences between clodronate and control in the proportion of patients who developed bone metastases (p=0.044) and in metastasis-free survival (p=0.022) (33). In contrast, there were no significant differences in either the incidence of bone metastases or five-year skeletal disease-free rate in the trial by Saarto et al (32). In a paper published in 2001, they reported that 21% of patients in the clodronate group and 17% in the control group had developed bone metastases (p=0.27). Data from a large double-blind trial of two years of treatment with clodronate were reported in a recent paper by Powles et al (34). Although the observed incidence of bone metastases was lower in the clodronate group (12% vs. 15% with placebo, data from published trial report), the p-value on the difference between clodronate and placebo over the five-year follow-up period was not statistically significant (hazard ratio [HR], 0.77; 95% CI, 0.56 to 1.08; p=0.127). However, when the analysis was restricted to the two-year treatment period, the hazard ratio was 0.44 (95% CI, 0.22 to 0.86; p=0.016). These data were reported as the final analysis for a trial that was designed to have the power to detect a 50% reduction in the incidence of bone metastases at three years and a 25% reduction at five years.

The Cochrane reviewers pooled the data presented in Table 7, using the fixed-effects model, and detected a significant difference in favour of clodronate (RR for bone metastasis, 0.73; 95% CI, 0.55 to 0.98; p=0.04) (6). However, there was significant heterogeneity among results from the trials (p_HET=0.035), which the Cochrane reviewers postulated might be due to differences in the study populations in the Diel and Saarto trials (32,33), or to the small number of events available for analysis. Re-analysis by the Cochrane reviewers, using the random-effects model, gave non-significant results (RR, 0.72; 95% CI, 0.41 to 1.26), demonstrating that the observed results are not robust to different statistical approaches.

**Table 7.** Randomized trials of bisphosphonates as adjuvant therapy in women with early-stage breast cancer.

<table>
<thead>
<tr>
<th>1st author, year (reference)</th>
<th># patients randomized (# evaluable)</th>
<th>Treatment groups</th>
<th>Median follow-up (months)</th>
<th>Radiological evidence of bone metastasis* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saarto, 2001 (32)</td>
<td>299 (282)</td>
<td>oral clodronate, 1.6 g/day observation</td>
<td>not reported</td>
<td>19% (16%)</td>
</tr>
<tr>
<td>Diel, 2000 (33) [abstract]</td>
<td>302 (302)</td>
<td>oral clodronate, 1.6 g/day observation</td>
<td>53</td>
<td>8% (17%)</td>
</tr>
<tr>
<td>Powles, 2002 (34)</td>
<td>1079 (1069)</td>
<td>oral clodronate, 1.6 g/day placebo</td>
<td>66</td>
<td>5% (8%)</td>
</tr>
</tbody>
</table>

* data from Cochrane review and meta-analysis (6)

**Survival**

Overall survival was significantly longer with clodronate than control in the trials by Diel et al (p=0.001) (47) and Powles et al (p=0.047) (34) and significantly shorter in the trial by Saarto et al (p=0.009) (32). In spite of significant heterogeneity between results from the trials
(p_{HET}<0.00001), the Cochrane reviewers pooled survival data from the Diel and Saarto trials. The meta-analysis did not detect a difference between clodronate and control in overall survival (RR for death, 0.97; 95% CI, 0.69 to 1.35) (6).

Survival curves for the large trial by Powles et al (34) were published after the Cochrane meta-analysis. When the Breast Cancer DSG added the numbers of deaths in the Powles trial to the meta-analysis, the pooled mortality risk ratio favoured clodronate over control but was not statistically significant (RR, 0.83; 95% CI, 0.69 to 1.01; p=0.06). There was still significant heterogeneity among trials (p_{HET}=0.0001).

Additional data will be available from the ongoing NSABP B-34 trial of adjuvant clodronate versus placebo, which aims to recruit 2,400 women over four years.

### Adverse Effects of Bisphosphonates

**Original 2002 Evidence Summary**

The most common adverse effects reported from the randomized trials of bisphosphonates versus control described above are summarized in Table 8. Toxicity data were generally not categorized by severity grade in the trial reports.

The majority of studies listed in Table 8 failed to demonstrate that oral clodronate is associated with appreciably more gastrointestinal upset than placebo (13,15,17,30). The exception was the Powles trial, which found that rates of diarrhea were significantly higher with clodronate than with placebo (p<0.001).

Van Holten-Verzantvoort et al did not report detailed toxicity data from their trial of oral pamidronate versus control, but did note that 23% of the pamidronate group withdrew early from the trial because of gastrointestinal complaints and a further 6% withdrew for this reason later (31). Theriault et al noted that injection-site reactions occurred in 6% of the pamidronate group and 0.5% in the placebo group (20). Conte et al reported phlebitis or tenderness at the infusion site in 12% of the pamidronate group and 5% of the control group (22). Local reactions at the injection site were more common with pamidronate than with zoledronate (4% vs. 1%) in a trial by Berenson et al (28).

Berenson et al compared three doses (0.4, 2.0 or 4.0 mg) of intravenous zoledronate to pamidronate in women with bone metastases from breast cancer (28). They noted skeletal pain as an adverse event in 49% of those treated with zoledronate and 60% on pamidronate. In a similar trial by Rosen et al, bone pain as an adverse event was reported by 54% of patients on zoledronate and 55% on pamidronate (27). Renal and urinary treatment-related adverse events were reported for 0.5% of patients on 4 mg of zoledronate, administered as a 15-minute infusion, and 0.2% on pamidronate in the Rosen trial (27). Grade 3 creatinine values were reported for one patient in each zoledronate group (5-minute infusion) and two in the pamidronate group in the Berenson trial (28).

One of 182 patients treated with intravenous pamidronate in the Theriault trial (20) and one of 73 in the Berenson trial (28) discontinued treatment because of allergic eye reactions. Three papers have described ocular complications related to bisphosphonates, predominately with pamidronate, outside of the clinical trial setting (48-50).

By 1994, the Ciba-Geigy Central Epidemiology and Drug Safety Centre had received 23 reports of suspected ocular adverse drug reactions associated with the use of intravenous pamidronate (48). Anterior uveitis, bilateral in six of seven patients, occurred within 24 to 48 hours after the drug was administered and recurred in four of the five patients who were rechallenged. In three other cases, unilateral episcleritis or scleritis occurred within one to six days after the administration of the drug. One patient with episcleritis was rechallenged five months later and experienced recurrence in the same eye. Thirteen patients reported nonspecific transitory conjunctivitis within six to 48 hours after administration of intravenous pamidronate, which was positive on rechallenge in six of eight patients. The severity of the
uveitis varied from minimal to severe, with recovery times ranging from one day to one month.

In 1995, O'Donnell et al (49) described a further two cases of patients with Paget’s disease who developed uveitis with intravenous pamidronate. Both had a good outcome after treatment with topical steroids. The authors suggested that patients on bisphosphonates who develop any new ocular symptoms should be referred to an ophthalmologist for urgent slit lamp examination to exclude any sight-threatening condition. The use of topical corticosteroids should be considered following this examination.

Rey et al reviewed reports between 1994 and 1999 and listed 11 additional cases of anterior uveitis and one of retrobulbar optic neuropathy with pamidronate, and three cases of ocular inflammation with alendronate (50). They noted that of 16 cases of pamidronate-induced uveitis, including those described in the 1994 report, 11 were bilateral and five unilateral.

**Updated 2004 Evidence Summary**

Updated safety results to the trial reported by Rosen et al were consistent with those previously reported; after 25 months of follow-up, reports of bone pain and renal/urinary adverse events were not significantly different for women receiving pamidronate compared with zoledronate (3u).

An extended safety profile for the trial reported by Powles et al (34) has been published (5u). At a median follow-up of 3.5 years after completion of medication (total study period: 5.5 years), the overall incidence of adverse events was not different for the women receiving clodronate compared with those receiving placebo; however, similar to the previous report, there was a higher incidence of gastrointestinal disorders, due mainly to diarrhea, in the women who received clodronate versus placebo (66% vs. 56.2%; 95% CI, 4.0 to 15.6; p<0.05).
Table 8. Adverse effects - randomized trials of bisphosphonate versus no bisphosphonate in women with breast cancer.

<table>
<thead>
<tr>
<th>1st author, year (reference)</th>
<th>Treatment groups</th>
<th>Nausea/Vomiting (%)</th>
<th>Diarrhea (%)</th>
<th>Asymptomatic hypocalcemia (%)</th>
<th>Other (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral bisphosphonates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubiana-Hulin, 2001 (13)</td>
<td>oral clodronate 1.6 g placebo</td>
<td>10 13</td>
<td>6 0</td>
<td>not reported</td>
<td>-</td>
</tr>
<tr>
<td>Kristensen, 1999 (14)</td>
<td>oral clodronate 1.6 g observation</td>
<td>not reported</td>
<td>not reported</td>
<td>27 4</td>
<td>-</td>
</tr>
<tr>
<td>Paterson, 1993 (15)</td>
<td>oral clodronate 1.6 g placebo</td>
<td>21 20</td>
<td>6 2</td>
<td>not reported</td>
<td>-</td>
</tr>
<tr>
<td>O’Rourke, 1995 (17)</td>
<td>oral clodronate 0.4 g</td>
<td>15</td>
<td>5</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Paterson, 1993 (15)</td>
<td>oral clodronate 1.6 g placebo</td>
<td>16</td>
<td>16</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Paterson, 1993 (15)</td>
<td>oral clodronate 3.2 g placebo</td>
<td>20</td>
<td>5</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>O’Rourke, 1995 (17)</td>
<td>oral clodronate 1.6 g placebo</td>
<td>29</td>
<td>5</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Kanis, 1996 (30)</td>
<td>oral clodronate 1.6 g placebo</td>
<td>not reported</td>
<td>not reported</td>
<td>7 0</td>
<td>-</td>
</tr>
<tr>
<td>Powles, 2002 (34,5u)</td>
<td>oral clodronate 1.6 g placebo</td>
<td>med: 22; f/u: 7 med: 23; f/u: 10</td>
<td>med: 15; f/u: 8 med: 7; f/u: 4</td>
<td>not reported</td>
<td>-</td>
</tr>
<tr>
<td><strong>Intravenous bisphosphonates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martoni, 1991 (11)</td>
<td>iv clodronate 300 mg placebo</td>
<td>not reported</td>
<td>not reported</td>
<td>0 0</td>
<td>-</td>
</tr>
<tr>
<td>Hultborn, 1999 (19)</td>
<td>iv pamidronate 60 mg placebo</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
<td>myelotoxicity: 1.5% vs. 0.5%</td>
</tr>
<tr>
<td>Theriault, 1999 (20,42)</td>
<td>iv pamidronate 90 mg placebo</td>
<td>vomiting &gt;10% more frequent with pamidronate than placebo</td>
<td>not reported</td>
<td>2% 2%</td>
<td>fatigue &gt;10% more common with pamidronate</td>
</tr>
<tr>
<td>Hortobagyi, 1998 (21,42)</td>
<td>iv pamidronate 90 mg placebo</td>
<td>not reported</td>
<td>not reported</td>
<td>0.5% 0</td>
<td>-</td>
</tr>
<tr>
<td>Conte, 1996 (22)</td>
<td>iv pamidronate 45 mg observation</td>
<td>not reported</td>
<td>not reported</td>
<td>17% 6%</td>
<td>fever: 5% vs. 3%</td>
</tr>
</tbody>
</table>

Abbreviations: med, medication period; f/u, follow-up period.
Dose and Route of Administration

**Dose**

Three of the trials discussed above randomized patients to one of several doses of the bisphosphonate under investigation (17,27,28). Three additional randomized trials compared different doses of bisphosphonates but did not include a control group (35-37).

O’Rourke et al detected no significant differences in pain scores or adverse events among three doses of oral clodronate (400 mg, 1600 mg, and 3200 mg) but noted one case of transient asymptomatic hypocalcemia in the 3200 mg group (17).

Glover et al randomized 61 women with bone metastases from breast cancer to one of four 12-week intravenous pamidronate regimens: 30 mg every two weeks, 60 mg every four weeks, 60 mg every two weeks, or 90 mg every four weeks (35). Although they noted no change from baseline pain score with the 30 mg dose and decreases in pain with the other doses, no formal statistical comparison was made among groups. There were no significant differences among dose groups in change from baseline for narcotic score. In a double-blind randomized trial, Koberle et al compared doses of intravenous pamidronate of 60 mg and 90 mg, given for up to six three-week cycles to 70 patients with pain from bone metastases (42 with breast cancer, 16 myeloma, and 12 other tumours) (36). They detected no significant difference between doses in pain intensity or quality of life. In a randomized trial that included 56 patients with breast cancer and 13 with lung, rectal or kidney cancer, Cascinu et al observed decreases in pain, mobility and analgesic scores with three doses of pamidronate (45 mg, 60 mg, and 90 mg every three weeks for 12 weeks), but did not report any significant differences among dose groups (37). Both Glover and Cascinu observed that pain scores improved more quickly (i.e., six weeks after the start of treatment) with the 90 mg dose compared to lower doses (35,37).

Rosen et al and Berenson et al conducted randomized trials that compared zoledronate at doses ranging from 0.4 to 8 mg to pamidronate (27,28). At a dose of 0.4 mg, zoledronate was significantly less effective at reducing skeletal events and the need for radiation therapy than pamidronate or higher doses of zoledronate (28). Rosen et al stopped using the 8 mg dose of zoledronate, in their trial of 4 mg versus 8 mg versus pamidronate, because of concerns about renal impairment (27).

**Oral versus Intravenous Administration**

One randomized trial, reported only in abstract form, compared equipotent doses of clodronate given orally or intravenously to women with bone metastases from breast cancer (26). During 18 months of follow-up, 10% of patients on oral clodronate and 18% on intravenous clodronate had vertebral fractures. Pain reduction was 25% with intravenous clodronate and 15% with oral clodronate, but the unit of measurement was not described.

V. INTERPRETIVE SUMMARY

**Original 2002 Interpretation**

There is abundant evidence from randomized controlled trials that oral clodronate or intravenous pamidronate can significantly reduce skeletal events and pain in women with breast cancer that is metastatic to bone. In direct comparisons, zoledronate at a dose of 4 mg was equivalent to pamidronate 90 mg, given intravenously every three to four weeks.

There is no information that can be used to answer two important clinical questions: i) Is it appropriate to continue bisphosphonates indefinitely? ii) Is it appropriate to switch from clodronate to pamidronate if a skeletal event occurs? No clinical trials have addressed the optimal duration of bisphosphonate use. Although the ASCO guidelines recommend continuation of pamidronate until there is a substantial decline in performance status, it is not known whether it is beneficial to continue bisphosphonates in patients who continue to experience
skeletal events. In view of the cost of prolonged bisphosphonate therapy, this topic would be an appropriate area for future research.

The ASCO guidelines recommend bisphosphonates only for patients with lytic disease (including those diagnosed on CT scans). The largest bisphosphonate trials (15,20,21) restricted entry to patients with at least one lytic bone metastasis (method of imaging not specified). There is no evidence to support or refute the use of bisphosphonates in patients with breast cancer metastases that are exclusively sclerotic. Since purely sclerotic metastases are very uncommon, the question of efficacy in this subgroup is unlikely to be answered by future randomized trials.

Randomized trials provide no evidence to suggest that skeletal events are reduced in patients with locally advanced breast cancer or breast cancer that is metastatic to sites not including bone.

There is limited and conflicting evidence concerning the use of bisphosphonates to prevent events in patients with early-stage breast cancer.

Randomized controlled trials support the use of oral or intravenous clodronate as part of a pain management program for bony metastatic disease from a variety of different tumour types, including breast cancer.

There is inconsistent evidence that treatment with bisphosphonates influences quality of life but consistent evidence that the toxicity of this drug class is minimal for most patients and is rarely serious.

A meta-analysis indicates that bisphosphonates do not measurably prolong survival in patients with bone metastases. There is conflicting evidence about whether oral clodronate can prolong survival when given as adjuvant therapy. The NSABP B-34 study will address this question.

Updated 2004 Interpretation
In direct comparisons, zoledronate at a dose of 4 mg was equivalent to pamidronate at 90 mg with respect to the primary efficacy variable, which was the proportion of patients who experienced a skeletal related event not including hypercalcemia. Longer follow-up confirms the safety of both bisphosphonates and the equivalence in skeletal event rates.

Retrospective analyses have been undertaken in two papers to look at the subgroup of only breast cancer patients or only breast cancer patients with at least one lytic metastasis at study entry. Both publications included an analysis that took into account the occurrence of more than one skeletal related event per patient. Although there was no difference in the primary efficacy variable, those “multiple event” analyses showed statistically significant differences in favour of the zoledronate arm. The conclusions of those papers are weakened by the fact that the analyses were unplanned. The additional analyses raise the possibility that zoledronate is more efficacious than pamidronate in reducing skeletal related events other than hypercalcemia, but they do not constitute convincing evidence. Although superiority for zoledronate is plausible based upon the results from a comparison in patients with hypercalcemia (8u), no difference in the suppression of bone resorption, as indicated by the N-telopeptide/creatinine ratio, was reported.

Ibandronate, given either orally or intravenously also reduces skeletal events but is currently not commercially available.

VI. ONGOING TRIALS
The Physician Data Query (PDQ) clinical trials database (http://www.cancer.gov/search/clinical_trials/) was searched for reports of new or ongoing trials. Only one trial was identified (9u).
NLM Identifier: NCT00009945;
Sponsors: National Surgical Adjuvant Breast and Bowel Project, National Cancer Institute, Southwest Oncology Group, North Central Cancer Treatment Group.
Projected accrual: 3,200.
Title/description: Phase III randomized double-blind placebo-controlled study of adjuvant clodronate with or without systemic chemotherapy and/or tamoxifen in women with early-stage breast cancer.

VII. DISEASE SITE GROUP CONSENSUS PROCESS
In 2002, the Breast Cancer DSG reviewed the updated and rewritten guideline report, which incorporated new evidence on the long-term use of oral clodronate and on adjuvant bisphosphonates, as well as data from two trials comparing zoledronate to pamidronate. The scope of the revised guideline was similar to the original but the single guideline question “Should bisphosphonates be used in patients with bone metastases from breast cancer?” was expanded to three: one related to patients with bone metastases, one to patients with advanced disease but no bone metastases, and one to the adjuvant use of bisphosphonates. The DSG suggested that the questions be further modified to include the outcomes of interest in each of these three settings. They also identified a need for more discussion on gastrointestinal toxicity and any new evidence presented at the 2002 ASCO meeting.

The DSG noted that it is uncertain whether bisphosphonate therapy can prevent skeletal complications in patients with a short life expectancy (less than 4 to 6 months), because the largest studies excluded these patients. Although the median time to first skeletal event was shorter than six months in the pamidronate studies that provide the best available evidence, the data do not show a difference emerging between pamidronate and control until approximately six months after study entry. The data suggest that the use of bisphosphonates to prevent skeletal events will require a considerable duration of administration. In contrast, pain relief can occur within days when bisphosphonates are used as an adjunct for pain control. Ultimately, the decision about whether or not it is appropriate to offer therapy when survival may be short rests with the treating physician.

DSG members discussed the use of clodronate in patients who have difficulty tolerating oral medications because of existing nausea, vomiting or esophagitis. The DSG strongly advocated that such patients should be spared a trial of oral clodronate before being offered intravenous pamidronate. Two DSG members suggested extending this recommendation to patients without nausea or vomiting, but in whom there is a high likelihood of gastrointestinal upset related to any medication, as well as patients who are likely to develop nausea, vomiting or esophagitis from planned radiotherapy or emetogenic medication. Other DSG members felt that predicting which patients may develop these problems would be difficult and that they could be managed by a brief interruption of oral clodronate or by switching to intravenous pamidronate at the next cycle of chemotherapy.

The DSG agreed that the revised guideline should include four new recommendations, in addition to those made in 1998:
1. Patients with a short expected survival (i.e., less than 6 months) who have well controlled bone pain may be an exception to the recommendation for bisphosphonates in women with bone metastases from breast cancer.
2. Patients with bone metastases from breast cancer who have difficulty tolerating oral medications (e.g., those with nausea/vomiting or esophagitis) should be offered intravenous pamidronate, without a trial of oral clodronate.
3. Intravenous zoledronate is an alternative to pamidronate when a shorter infusion time (15 minutes) is important.
4. Bisphosphonates are not recommended to prevent bone metastases in women with locally advanced breast cancer or non-skeletal metastases.

The DSG considered extending their recommendations to men with breast cancer. No randomized trials have assessed the efficacy of bisphosphonates in men with breast cancer, but men have participated in randomized trials of bisphosphonates for multiple myeloma (27,55-59). Since there is no evidence to suggest that the benefit in multiple myeloma is gender specific, it is reasonable to recommend the use of bisphosphonates in men with breast cancer that is metastatic to bone. The DSG also noted that there was no evidence for continuing or switching bisphosphonates after a skeletal event. Qualifying statements were added to the recommendations to address these two issues.

VIII. ECONOMIC EVALUATION

A systematic review of the evidence on the costs and cost-effectiveness of bisphosphonates is outside the scope of this guideline report. The clinical recommendations made in this practice guideline are based on a systematic review of the research evidence, an interpretation of this evidence in the context of cancer care in Ontario, consensus by members of the Breast Cancer DSG, and external review by Ontario clinicians. Economic evaluation is not an explicit step in the guideline development process but may be considered by other groups in the cancer care system, such as policy makers, as supplementary information.

The Breast Cancer DSG is aware of four relevant economic evaluations, one on clodronate (51) and three on pamidronate (52-54). Only one economic evaluation was based on Canadian data (53). The others were conducted in the United States (51,54) and Switzerland (52), and may not apply to Ontario because conclusions from economic evaluations can be highly sensitive to costs, which vary significantly from country to country.

IX. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Practice Guideline

Based on the original evidence, which was available up to August 2002, the Breast Cancer DSG drafted the following practice guideline:

Target Population

Patients with breast cancer.

Original 2002 Draft Recommendations

- **Women with breast cancer who have bone metastases** should be offered treatment with oral clodronate or intravenous pamidronate.
  - An exception may be patients with a short expected survival (i.e., less than 6 months) who have well controlled bone pain.
  - Patients who have difficulty tolerating oral medications (e.g., those with nausea/vomiting or esophagitis) should be offered intravenous pamidronate.
  - Intravenous zoledronate is an alternative to pamidronate when a shorter infusion time (15 minutes) is important.
  - Intravenous clodronate has not been examined for its ability to reduce morbidity of bone metastases with long-term use. When clodronate is used for this purpose, the oral route is recommended.

- **In patients with bone metastases and pain**, pamidronate, zoledronate or clodronate may be a useful adjunct to conventional measures for pain control.

- Bisphosphonates are not recommended to prevent bone metastases or improve survival in **women with locally advanced breast cancer or non-skeletal metastases**.
Current evidence is insufficient to support the use of bisphosphonates as adjuvant therapy to either prevent skeletal events or improve survival in women with early-stage breast cancer.

**Qualifying Statements**
- There is no evidence from clinical trials that address the optimal duration of bisphosphonate use.
- There are no data on the efficacy of bisphosphonates in men with breast cancer, but men have participated in randomized trials of bisphosphonates for multiple myeloma. Since there is no evidence to suggest that the benefit detected in multiple myeloma trials is gender specific, it is reasonable to recommend the use of bisphosphonates in men with breast cancer that is metastatic to bone.

**Practitioner Feedback**
Based on the evidence described in the original 2002 report and the draft recommendations presented above, feedback was sought from Ontario clinicians in October 2002.

**Methods**
Practitioner feedback was obtained through a mailed survey of 127 practitioners in Ontario (88 Medical Oncologists and 39 Radiation Oncologists). The survey consisted of 21 questions about the quality of the practice-guideline-in-progress (PGiP) report and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Breast Cancer DSG reviewed the results of the survey.

**Results**
Sixty-seven responses were received out of the 127 questionnaires sent (53% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 53 indicated that the report was relevant to their clinical practice, and they completed the questionnaire. Key results of the practitioner feedback survey are summarized in Table 9.
Table 9. Practitioner responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
<th>Strongly agree or agree</th>
<th>Neither agree nor disagree</th>
<th>Strongly disagree or disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>The rationale for developing a clinical practice guideline, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>53 (100%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>50 (94%)</td>
<td>2 (4%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>50 (94%)</td>
<td>3 (6%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>52 (98%)</td>
<td>1 (2%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>53 (100%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>50 (94%)</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
<td></td>
</tr>
<tr>
<td>This PGIP report should be approved as a practice guideline.</td>
<td>51 (96%)</td>
<td>0</td>
<td>2 (4%)</td>
<td></td>
</tr>
</tbody>
</table>

If this PGIP report were to become a practice guideline, how likely would you be to make use of it in your own practice?

<table>
<thead>
<tr>
<th></th>
<th>Very likely or likely</th>
<th>Unsure</th>
<th>Not at all likely or unlikely</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>49 (92%)</td>
<td>1 (2%)*</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

* plus 1 (2%) missing

Summary of Written Comments
Nine respondents (19%) provided written comments. The main points contained in the written comments were:
1. Is there any evidence that bisphosphonates are useful in women with purely osteoblastic metastases?
2. Practitioners asked for more information on the relative cost-effectiveness of different bisphosphonates (oral clodronate, iv pamidronate, iv zoledronate). They also commented on the current funding policies in Ontario related to the use of bisphosphonates for breast cancer.

Modifications/Actions Based on the October 2002 Practitioner Feedback
The DSG discussed the issues described above and responded as follows:
1. There is insufficient evidence to support or refute the use of bisphosphonates in patients with purely osteoblastic metastases from breast cancer. Three randomized trials included a small number of breast cancer patients with only osteoblastic metastases (11,14,19), but most trials were limited to those with lytic or mixed lytic/sclerotic bone metastases (13,15-17,20-22,26-28). The ASCO guideline recommended intravenous pamidronate for women with metastatic breast cancer who have lytic destruction of bone on plain radiographs or a CT scan, but the Ontario guideline does not restrict its recommendations to patients with osteolytic metastases. Because only about 15% of women with bone metastases from breast
cancer have purely osteoblastic lesions, randomized trials restricted to this population are unlikely to be conducted. In the absence of evidence from randomized trials in this population, the DSG chose to generalize the evidence available and to recommend that treatment with bisphosphonates should be offered to all women with breast cancer who have bone metastases.

2. Economic, funding and policy issues are outside the scope of the guideline-development cycle, which is based on a systematic review of the evidence related to clinical benefits and harms. Please see the Economic Evaluation section above for further information.

No changes were made to the recommendations as a result of feedback from practitioners, but the DSG’s assessment of the evidence for bisphosphonate use in patients with osteoblastic lesions was added to the Interpretive Summary.

Practice Guidelines Coordinating Committee Approval Process
The 2002 practice guideline report was then circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Seven members of the PGCC returned ballots. All seven PGCC members approved the practice guideline report as written. One member approved the guideline and provided suggestions for consideration by the Breast Cancer DSG.

X. PRACTICE GUIDELINE
This practice guideline reflects the most current information reviewed by the Breast Cancer DSG.

Target Population
These recommendations apply to women with breast cancer.

Original 2002 Practice Guideline Recommendations
These practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the 2002 external review process. They were approved by the Breast Cancer DSG and the Practice Guidelines Coordinating Committee.

- **Women with breast cancer who have bone metastases** should be offered treatment with oral clodronate or intravenous pamidronate.
  - An exception may be patients with a short expected survival (i.e., less than six months), who have well controlled bone pain.
  - Patients who have difficulty tolerating oral medications (e.g., those with nausea/vomiting or esophagitis) should be offered intravenous pamidronate.
  - Intravenous zoledronate is an alternative to pamidronate when a shorter infusion time (15 minutes) is important.
  - Intravenous clodronate has not been examined for its ability to reduce morbidity from bone metastases with long-term use. When clodronate is used for this purpose, the oral route is recommended.
- **In patients with bone metastases and pain**, treatment with pamidronate, zoledronate, or clodronate may be a useful adjunct to conventional measures for pain control.
- Bisphosphonates are not recommended to prevent bone metastases or improve survival in **women with locally advanced breast cancer or non-skeletal metastases**.
- Current evidence is insufficient to support the use of bisphosphonates as **adjuvant therapy** to either prevent skeletal events or improve survival in **women with early-stage breast cancer**.
Modifications to the 2002 Recommendations Based on the 2004 Update

In 2004, the DSG decided that the following minor changes would make the first recommendation clearer:

1. Intravenous zoledronate was listed as a third bisphosphonate (main bullet and second sub-bullet) appropriate for women with breast cancer who have bone metastases. This option was already implied in the third sub-bullet of the recommendation.

2. The infusion time for intravenous pamidronate was added to the third sub-bullet, which recommended intravenous zoledronate when a shorter infusion time was important.

These modifications were not circulated for external review because the revised recommendations did not deviate substantially from the original recommendations. The modified recommendations are listed below.

Updated 2004 Practice Guideline Recommendations

These practice guideline recommendations reflect the integration of the 2002 draft recommendations, feedback obtained from the 2002 external review process, and modifications made during the 2004 update.

- **Women with breast cancer who have bone metastases** should be offered treatment with oral clodronate, intravenous pamidronate, or intravenous zoledronate.
  - An exception may be patients with a short expected survival (i.e., less than six months), who have well controlled bone pain.
  - Patients who have difficulty tolerating oral medications (e.g., those with nausea/vomiting or esophagitis) should be offered intravenous pamidronate or zoledronate.
  - Intravenous zoledronate may be preferable to pamidronate when a shorter infusion time (15 minutes versus two hours, respectively) is important.
  - Intravenous clodronate has not been examined for its ability to reduce morbidity from bone metastases with long-term use. When clodronate is used for this purpose, the oral route is recommended.

- **In patients with bone metastases and pain**, treatment with pamidronate, zoledronate, or clodronate may be a useful adjunct to conventional measures for pain control.

- Bisphosphonates are not recommended to prevent bone metastases or improve survival in women with locally advanced breast cancer or non-skeletal metastases.

- Current evidence is insufficient to support the use of bisphosphonates as adjuvant therapy to either prevent skeletal events or improve survival in women with early-stage breast cancer.

Qualifying Statements

- There is no evidence from clinical trials that address the optimal duration of bisphosphonate use.
- There are no data on the efficacy of bisphosphonates in men with breast cancer, but men have participated in randomized trials of bisphosphonates for multiple myeloma. Since there is no evidence to suggest that the benefit detected in multiple myeloma trials is gender specific, it is reasonable to recommend the use of bisphosphonates in men with breast cancer that is metastatic to bone.

Related Guidelines

- (in development) Practice Guideline #3-14: The Use of Bisphosphonates in Men with Hormone-Refractory Prostate Cancer

JOURNAL REFERENCE
An earlier version of this practice guideline report was completed in 1998 and published as:


XI. ACKNOWLEDGEMENTS
The Breast Cancer Disease Site Group would like to thank the following individuals for their contribution: Dr. David Warr and Mary Johnston for taking the lead in writing this practice guideline report and Dr. David Warr, Dr. Mark Clemens, and Susan Sinclair for updating it.

For a complete list of members of the Breast Cancer Disease Site Group, please visit the Cancer Care Ontario website at http://www.cancercare.on.ca/.
REFERENCES


Update


EBS 1-11 Document Assessment and Review Tool.

**DOCUMENT ASSESSMENT AND REVIEW TOOL**

<table>
<thead>
<tr>
<th>Number and title of document under review</th>
<th>1-11 Use of Bisphosphonates in Women with Breast Cancer</th>
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<tr>
<td>Date of current version</td>
<td>April 2004</td>
</tr>
<tr>
<td>Clinical reviewer</td>
<td>Dr. M. Clemons</td>
</tr>
<tr>
<td>Research coordinator</td>
<td>Chika Agbassi</td>
</tr>
<tr>
<td>Date DART initiated</td>
<td>11 May 2010, was on hold until San Antonio 2010, reinitiated</td>
</tr>
<tr>
<td>Date and final results / outcomes</td>
<td>2 December 2011 [UPDATE]</td>
</tr>
</tbody>
</table>

Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.

1. **Is there still a need for a guideline covering one or more of the topics in this document as is?** Answer Yes or No, and explain if necessary:
   - **1. YES**
     - If No, then the document should be **ARCHIVED** with no further action; **go to 11.** If Yes, then **go to 2.**

2. **Are all the current recommendations based on the current questions definitive or sufficient, and have less than 5 years elapsed since the latest search?** Answer Yes or No, and explain if necessary:
   - **2. NO**
     - We expect some new data since the last guideline.
     - If Yes, the document can be **ENDORSED** with no further action; **go to 11.** If No, **go to 3.**

3. **Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed?** Answer Yes or No, and explain if necessary, providing references of known evidence:
   - **3. NO**
     - If Yes, the document should be taken off the website as soon as possible. A **WARNING** should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, **go to 4.**

4. **Do current resources allow for an updated literature search to be conducted at this time?** Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:
   - **4. YES**
     - There is a designated research co-ordinator at the PEBC to carry out the literature search
     - If No, a **DEFERRAL** should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, **go to 5.**

5a. **Guideline Research Questions.** Please review the original guideline research questions below and if applicable, list any MINOR changes to the questions that now must be considered. If a question is no longer relevant, it can be deleted. The DART process evaluates the guideline as is and CANNOT accommodate significant changes to the questions or the addition of new questions introducing new patient populations or new agents/interventions because if this what is required in order to make this guideline relevant, then a brand new document should be produced and this guideline as is should be **ARCHIVED** (i.e., go back to Q1 of this DART form and answer NO). **[Changes are in BOLD]**

**Changes to the original research questions:**
- Add 2 new research Qs
  - Can we identify patients at different risks of skeletal-related events so that the frequency of administration of bisphosphonates can be adjusted to reflect their use in the modern era?
  - Should bisphosphonates be used to reduce the risk of cancer therapy induced bone loss in women with early stage breast cancer?
Original Questions:
Should bisphosphonates be used to reduce pain, reduce the likelihood of skeletal events other than hypercalcemia (i.e., fractures, requirement for radiation therapy, surgery), improve quality of life, or improve survival in women with bone metastases due to breast cancer?

Can we identify patients at different risks of skeletal-related events so that the frequency of administration of bisphosphonates can be adjusted to reflect their use in the modern era?

Should bisphosphonates be used to reduce the likelihood of bone metastases or to improve survival in women with breast cancer that is locally advanced or metastatic to sites other than bone?

Should bisphosphonates be used to reduce the risk of bone metastases or improve survival in women with early stage breast cancer?

Should bisphosphonates be used to reduce the risk of cancer therapy induced bone loss in women with early stage breast cancer?

Target population:
These recommendations apply to women with breast cancer.

5b. List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence). [Changes are in BOLD]

Changes to the selection criteria:
- Given the vast amount of literature, included studies should be restricted to Phase 3 and randomised Phase 2 trials.

Inclusion criteria:
Articles were eligible if they met all of the following criteria:
1. They were published reports, or abstracts from the ASCO or SABSC meetings.
2. They presented results of a meta-analysis or randomized controlled trial (phase 2 or 3) that compared:
   i. treatment with a bisphosphonate to observation or placebo;
   ii. two bisphosphonates;
   iii. two or more doses of the same bisphosphonate; or
   iv. the same bisphosphonate given by two routes of administration.
3. Trial participants were primarily patients with breast cancer (early-stage or advanced) although trial participants could also include patients with other solid tumours or myeloma.
4. Results were reported, by treatment group, for at least one of the following outcomes: survival, quality of life, and adverse effects. Additional outcomes of interest for patients with bone metastases from breast cancer included bone pain (measured using a pain scale or analgesic consumption) and skeletal events, other than hypercalcemia (as bisphosphonates are acknowledged to be an effective intervention for this complication). The development of bone metastases was also an outcome of interest in patients without bone metastases at the time of randomization.

Evidence-based practice guidelines and systematic reviews addressing the guideline questions were also included.

Exclusion criteria:
None specified. Phase 1 trials and non-randomized trials were excluded.

5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.
Full Selection Criteria, including types of evidence (e.g., randomized, non-randomized, etc.):

Articles were eligible if they met all of the following criteria:

1. They were published reports, or abstracts from the ASCO or SABSC meetings.

2. They presented results of a meta-analysis or randomized controlled trial (phase 2 or 3) that compared:
   i. treatment with a bisphosphonate to observation or placebo;
   ii. two bisphosphonates;
   iii. two or more doses of the same bisphosphonate; or
   iv. same bisphosphonate different routes or frequencies of administration.

3. Trial participants were primarily patients with breast cancer (early-stage or advanced) although trial participants could also include patients with other solid tumours or myeloma.

4. Results were reported, by treatment group, for at least one of the following outcomes: survival, quality of life, and adverse effects. Additional outcomes of interest for patients with bone metastases from breast cancer included bone pain (measured using a pain scale or analgesic consumption) and skeletal events, other than hypercalcemia (as bisphosphonates are acknowledged to be an effective intervention for this complication). The development of bone metastases was also an outcome of interest in patients without bone metastases at the time of randomization.

Evidence-based practice guidelines and systematic reviews addressing the guideline questions were also included.

**Exclusion criteria:**

Phase 1 trials and non-randomized trials were excluded.

**Search Period:**

- March 2004 to March 2011 (Medline wk 4 and Embase wk 12)
- 2004 to November 2011 (ASCO Annual Meeting)
- 2006 to November 2011 (San Antonio BC Symposium)

**Brief Summary/Discussion of New Evidence:**

Of 984 total hits from the Medline + Embase and 45 total hits from ASCO + San Antonio conference abstract searches, 33 references representing 2 guidelines, 6 meta-analyses (4 full text publications and 2 abstracts) and 20 RCTs were found. 5 of the RCTs were already included in the existing guideline (rows highlighted in grey in the Table) and 15 RCT are new studies.

<table>
<thead>
<tr>
<th>Interventions (mg/m²)</th>
<th>Name of RCT</th>
<th>Population</th>
<th>Outcome</th>
<th>Brief results</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Bisphosphonate vs. Observation or Placebo</td>
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</tr>
<tr>
<td>Zoledronic acid (4mg q6mos x 12mos) vs. observation till T-score &lt; -2.5</td>
<td>Phase III KCSG-BR06-01 12mos</td>
<td>Pre-MW Age &gt; 40yrs T-score &gt; -2 (n=112)</td>
<td>*BMD BTM</td>
<td>BMD remained stable in the ZA with a mean change of -1.1% against -7.5% in the observation arm. BTM was significantly lower in ZA</td>
<td>Kim J. et al 2011</td>
</tr>
<tr>
<td>Risedronate- (35mg qW) + AI vs. Placebo + AI</td>
<td>SABRE (24mos)</td>
<td>Post-MW H-receptor +ve T-scores -1 to -2 (n=154)</td>
<td>BMD BTM</td>
<td>When compared to placebo, the RIS arm showed a significant change in baseline BMD: LS (2.2% vs. -1.8%; TR = 1.02) P&lt;0.0001 TH (1.8% vs. -1.1%; TR = 1.03) P&lt;0.0001</td>
<td>Van Poznak C. et al 2010</td>
</tr>
<tr>
<td>Risedronate (35mg/qk x 24mos) vs. Placebo</td>
<td>(24mos)</td>
<td>Post-MW CIM Primary BC + TAM, + AI Age &gt; 18 (n=87)</td>
<td>*BMD BTM</td>
<td>BMD: There was a significant difference between the groups. RIS arm showed an increase of 1.2% (spine) and 1.3% (hip) while the placebo arm showed a decrease of 0.9% (spine) and 0.8% (hip). P&lt;0.01. Women on RIS without Al had the greatest improvement in BMD at the hip (2.2% + 0.9%) p=0.05 BTM was significantly increased in the placebo arm and reduced RIS arm. P&lt;0.01</td>
<td>Van Long G. et al 2010</td>
</tr>
<tr>
<td>Clodronate (1600mg qd x 24mos)</td>
<td>ISRCTB3688802 Primary BC</td>
<td>*BTM</td>
<td>TH and LS BMD scores were significantly higher in</td>
<td>McCloskey S. et al 2007</td>
<td></td>
</tr>
</tbody>
</table>

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**Notes:**

- TR: Treatment ratio.
| vs. Placebo | 6 (24mos) | (n=851) | BMD | the CLO arm (1.92%) P=0.0001. CLO was associated with reduced BTM and greater protection against OBM. | E. et al 2010 | bl. | Zoledronic acid (4mg q3W x12mos) vs. Placebo | Phase II (3mos) | Stage II-III | Age >18 ECOG PS = 0 or 1 (n=120) | DTC | BTM DFS | DTC: At 3mos, the proportion of patients with detectable DTC was less in the ZOL arm than in placebo (P=0.054.) DFS and BTM did not show any significant difference between arms | Aft et al 2010 | Zoledronic acid (4mg q3mos x12mos) vs. Placebo | Observation | Post-MW Node +ve Stage II-III (n=68) | *BMD OS DFS | BMD: ZA significantly improved the BMD at LS by 4.28% +0.0; P=0.01; TF by 1.9% P=0.03; Trochanter by 2.97% P=0.03; Calceneum by 2% P=0.01 | Leal T. et al 2010 | Risedronate (35mg qW x 12mos) vs. Placebo | Phase III (12mos) | Stage I-IIIIB BMT score >2 (n=216) | BMD | The change in LS- BMD was not significantly different between arms. P= 0.18 | Hines et al 2009 | Ibandronate (6mg q4W x24mos) vs. Placebo | (24mos) | BM Age 58 ± 5yrs (n=150) | *SRE TSE | Compared with placebo, IBA significantly reduced the proportion of patients with SRE (36% vs. 48%) P=0.027 and the TSE (457d vs. 304d) P=0.007. IBA was shown to reduce the risk of SRE by 32% (HR 0.69; 95%CI 0.42-0.79) P= 0.003. | Heras et al 2009 | Clodronate (1.6g qd for 36mos) vs. Placebo | Observation | Pre & Post-MW Karnofsky-PS >70% (n=89) | BMD DFS | OS | OFS | SRE | FS | BMD | OS | DFS | The endocrine arms remained significantly lower in OS, OBM, and fracture. | BMD, BTM Fracture | There were no significant differences between arms in OS, OBM, and fracture. | Kristensen et al 2008 | Zoledronic Acid (4mg q3mos x) vs. Placebo | Phase III (24mos) | Pre-MW Mean Age = 42yrs (n=101) | *BMD, BTM Fracture | In the placebo arm, the LS and the TH BMD declined by 6.3% and 2.6% respectively but remained significantly stable in the ZA arm. -0.0001 BMT remained stable in the ZA arm. | Heshman et al 2010 | Heshman et al 2008 | Zoledronic acid (4mg q6mos x36mos) plus Goserelin + Tamoxifen or Al vs. Goserelin + Tamoxifen or Al | ABCSG-12 (60mos) | Post-MW Osteopenic T-scores -1 to -2.5 (n=50) | *BMD BTM Fracture | Compared to baseline BMD, ZA showed an increase at LS (4.0%; MD = 0.039g/cm^2, P=0.02) and trochanter (3.9%; MD = 0.028g/cm^2, P=0.07). The endocortical arms remained significantly lower compared to baseline with AI showing more bone loss than TAM | Gannt M. et al 2008 | Gannt M. et al 2007 | Morning zoledronic 4mg q4W x 4 vs. Zoledronic Night | women with BM Med age = 62 yrs (44) | BTM PTH | BTM was significantly decreased in both arms. PTH was significantly increased in both arms too but the increase was lower in the nightly ZA arm (p=0.001) | Generali D. et al 2008 | Clodronate 1600/d x2yr vs. std F/U | (103mos) | Med AGE - 51yrs | OBM OVM OS DFS | Improvement in survival was significantly (P=0.04) better in the CLO arm (20.4% deaths) compared with the std F/U arm (40.7%). At 103 mos, DFS and OBM did not retain the significant reductions previously observed at 36 and 55 mos | Diel et al 2008 | Ibandronate acid 6mg q3W or q4W x 60 to 96W vs. Placebo | 12mos | women with BM ECOG-PS <2 Age > 18yr (n=309) | serum creatinine | There was no significant difference between arms. | Body J.J. et al 2006 | Oral vs. IV bisphosphonate | Ibandronate 50mg/day x12wks vs. Zoledronic Acid 4mg q4w x12wk | 12wk | women with BM (n=275) | BTM | Both IBA and ZOL significantly reduced the BTM and oral IBA was shown not to be inferior to iv ZOL | Body J.J. et al 2007 | Immediate vs. Delayed Bisphosphonate | Zoledronic acid (4mg q6mos x 5yr) vs. Zoledronic acid (after PF or BMD <2) | ZO-FAST (36mos) | Post-MW Early BC 5 yrs Al therapy T-score > -2 | BMD | BMD: The mean change of the LS-BMD was significantly higher in the immediate arm (+4.39%) than the delayed arm (-4.9%). P<0.001. DFS: the RRR was shown to be 41% (p= 0.0314) in | Eidtmann et al 2010 | Bundert et al 2009 |
## EBS 1-11: TO BE UPDATED

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Outcome</th>
<th>Participants</th>
<th>Duration</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid (4mg q6mos) vs. Zoledronic acid(after PF or BMD &lt; -2)</td>
<td>Post-MW Stage I-III A EOCOG-PS 0-2 ≤ 6yrs TAM (n=558)</td>
<td>BMD: The mean change of the LS-BMD was significantly higher in the immediate arm (+3.66%) than the delayed arm (1.66%). P&lt;0.001. Toxicity: (fever, N/V, limb edema, ONJ, and fatigue)</td>
<td>(12mos)</td>
<td>Hines S. et al 2009</td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid (4mg q6mos) vs. Zoledronic acid(after PF or BMD &lt; -2)</td>
<td>Post-MW Stage I-III A EOCOG-PS ≤2 T-score &gt; -2 (n=301)</td>
<td>*BMD BTM</td>
<td>Z-FAST (12 mos)</td>
<td>Brunsky A. et al 2007</td>
<td></td>
</tr>
</tbody>
</table>

### Meta analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>RCTs</th>
<th>Outcome</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis of 8 RCTs</td>
<td>(n=6132)</td>
<td>OS, BMFS</td>
<td>OS in the BIS arm was significantly improved HR=0.808 (95%CI; 0.708-0.923) P&lt;0.022.</td>
</tr>
<tr>
<td>Meta-analysis of 14 RCTs</td>
<td>(n=7461)</td>
<td>Fracture</td>
<td>BIS use did not reduce the incidence of fracture in Early BC (OR=0.84, 95%CI= 0.65-1.09 P=0.197), Post-MW (OR = 0.82, 95%CI= 0.55-1.20 P=0.298) or Al therapy (OR= 0.79, 95%CI= 0.53-1.17 P=0.242), Heterogeneity was not significant.</td>
</tr>
<tr>
<td>Meta-analysis of 13 RCTs</td>
<td>(n=10,694)</td>
<td>ONJ</td>
<td>BIS use was significantly associated with ONJ when compared with no use: OR =3.23(95%CI = 1.7-8)</td>
</tr>
<tr>
<td>Meta-analysis of 18 RCTs</td>
<td>Metastatic-BC</td>
<td>SRE, PF, BR/BS</td>
<td>When compared with placebo; SRE: BIS was associated with reductions in all SRE. Heterogeneity was not significant ZOL; RR = 0.70 (95%CI, 0.64-0.90; p &lt;0.001) I² =28% PAM; RR = 0.81 (95%CI, 0.73-0.91; p =0.003) I² = 34% CLO; RR = 0.87 (95%CI, 0.75-1.00; p=0.05) I² = 0% PF: PAM was not significantly different from placebo but ZOL and CLO were associated with reduction in risk of PF. Heterogeneity was not significant. ZOL; RR = 0.60 (95%CI, 0.47-0.76; p&lt;0.001) I² = 0% CLO; RR = 0.76 (95%CI, 0.64-0.90; p=0.001) I² = 0% BR/BS: COL was not significantly different from placebo but ZOL and PAM were associated with reduction in risk of BR and BS. Heterogeneity was significant ZOL; RR = 0.67 (95%CI, 0.46-0.97; p=0.04) I² =68% PAM; RR = 0.72 (95%CI, 0.62-0.84; &lt;0.001) I² =28% BIS did not reduce mortality rate compared with placebo.</td>
</tr>
<tr>
<td>Meta-analysis of 8 Phase III RCTs</td>
<td>OS, BMFS, NSMF</td>
<td>There was no significant difference in OS, BMFS, and NSMFS between arms.</td>
<td>Ha TC, et al 2007</td>
</tr>
</tbody>
</table>

### Bisphosphonate therapy vs. Placebo or no therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Outcome</th>
<th>Participants</th>
<th>Duration</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risedronate vs. Placebo</td>
<td>Randomized, Double-blinded, Placebo Controlled Study to Assess Efficacy of Oral 35 mg Per Week Risedronate in Preventing Bone Loss in Postmenopausal Women With Aromatase Inhibitor Therapy for Breast Cancer</td>
<td>RCTs</td>
<td>recruiting</td>
<td>NCT00859703</td>
<td>November 18, 2009</td>
</tr>
<tr>
<td>Risedronate 35 mg weekly vs. Placebo</td>
<td>The Effect of Bisphosphonate on Bone Mass and Bone Turnover in Elderly, Postmenopausal Women With Breast Cancer Following Initiation of Aromatase Inhibitor Therapy</td>
<td>Recruiting</td>
<td>Active, not recruiting</td>
<td>NCT00485953</td>
<td>June 2011</td>
</tr>
<tr>
<td>Zoledronic Acid 4 mg q3W x8 injections vs. observation</td>
<td>Comparative Study of Neoadjuvant Chemotherapy With and Without Zometa for Management of Locally Advanced Breast Cancers</td>
<td>Recruiting</td>
<td>recruiting</td>
<td>NCT01367288</td>
<td>June 2011</td>
</tr>
</tbody>
</table>

On Going trials


**Note:** The table above summarizes the findings of various studies comparing bisphosphonate therapy versus placebo or no therapy in the context of breast cancer treatment. The studies vary in their methodologies, outcomes, and participants, reflecting the complex interactions between bisphosphonates and breast cancer treatment regimens.


**EBS 1-11: TO BE UPDATED**

<table>
<thead>
<tr>
<th>Zoledronic Acid 4mg qmos x 18mos vs. observation</th>
<th>A Multicenter, Open-label, Randomized Trial to Evaluate the Anti-cancer Effects of Zoledronic Acid and Circulating Tumor Cell Measurements in Patients With HER2-negative Metastatic Breast Cancer Without Bone Metastasis</th>
<th>recruiting</th>
<th>NCT0112933 6</th>
<th>September 1, 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic Acid qmos x 6mos → q3mos x 30mos vs. clodronate qd x35mos or oral ibandronate qd x35mos</td>
<td>Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer</td>
<td>Active, not recruiting</td>
<td>NCT0012720 5</td>
<td>September 21, 2010</td>
</tr>
<tr>
<td>Zoledronic Acid early vs. delayed</td>
<td>A Randomized, Controlled, Open-Label Trial of Empiric Prophylactic vs. Delayed Use of Zoledronic Acid for Prevention of Bone Loss in Postmenopausal Women With Breast Cancer Initiating Therapy With Letrozole After Tamoxifen</td>
<td>unknown</td>
<td>NCT0010726 3</td>
<td>June 16, 2010</td>
</tr>
<tr>
<td>Zoledronic Acid q3-4W x 6 doses, →q3mos x 6 doses, →q6mos x 5 doses vs. observation</td>
<td>Does Adjuvant Zoledronic Acid Reduce Recurrence in Patients With High Risk Localized Breast Cancer?</td>
<td>unknown</td>
<td>NCT0007202 0</td>
<td>November 9, 2011</td>
</tr>
</tbody>
</table>

Al= aromatase inhibitor; BC= breast cancer; BID= twice daily; BR/B= bone radiation or bone surgery; BM= bone metastasis; BMD= Bone mineral density; BMFS= Bone metastasis free survival; BTM= bone turnover marker; CIM= chemotherapy induced menopause; CLO= Clodronate; DFS= Disease free survival; DR= disease recurrence; DTC= Disseminated tumour cells; IBA= Ibandronate; LS= lumbar spine; mos= months; MW= menopausal women; n= number recruited; NSMFS= nonskeletal metastasis free survival; OBM= occurrence of bone metastasis; OSF= Osteoporotic free survival; ONJ= Osteonecrosis of the jaw; OR= odds ratio; OS= Overall survival; PF= pathologic fracture; q= every; RIS=Risedronate; RRR= relative risk reduction; SRE= Skeletal related events; TH= Total hip; TSE= time to skeletal event; TR= treatment ratio; vs.= versus; W= weeks; ZA= zoledronic acid

* Primary outcome → followed by

**New References Identified (alphabetical order):**


14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinical adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebo/
26. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. limit 36 to human
38. exp breast neoplasms/
40. (breast? or mammary).tw.
41. 39 and 40
42. 38 or 41
43. exp Diphosphonates/
44. (pamidronate or neridronate or olpadronate or alendronate or risedronate or zoledronate).tw.
45. 43 or 44
46. 42 and 45
47. (200402$ or 2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$).ed.
48. 46 and 47
49. 37 and 48

**Embase**
1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthesis$ or quantitative overview$).tw.
4. (systematic adj (review$ or overview$)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random$.tw.
18. (clinical adj trial$1).tw.
19. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
6. Is the volume and content of the new evidence so extensive such that a simple update will be difficult?

6. No

If Yes, then the document should be ARCHIVED with no further action; go to 11. If No, go to 7.

7. On initial review, does the newly identified evidence support the existing recommendations? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:

7. New evidence supports the exiting recommendations but current recommendations do not cover all relevant subjects. Regarding future guidelines for production by the Breast DSG:

- It would be useful to produce a guideline on all bone-targeted agents, not just bisphosphonates – particularly of interest is the new agent denosumab
- A vast amount of literature is expected on bone-targeted agents so it would be easier to handle if this is produced as 2 separate guidelines for:
  - early-stage breast cancer
  - metastatic breast cancer

It would also be useful to have another guideline to address the use of bone-targeted agents for cancer-therapy induced bone-loss.

- We now have ABCSG-12 which would support adj BP use
- Data will be presented at San Antonio showing that the frequency of BP in MBC can be reduced
- Italian data now also available
- There is a lot of denosumab data too
- B34 is also presented

If Yes, the document can be ENDORSED. If No, go to 8.
8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:

<table>
<thead>
<tr>
<th>8. NO but the scope should be broadened to include the use of bone-targeted agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>If Yes, a <strong>WARNING</strong> note will be placed on the web site. If No, go to 9.</td>
</tr>
</tbody>
</table>

9. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:

<table>
<thead>
<tr>
<th>9. NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>If Yes, the document update will be <strong>DEFERRED</strong>, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, go to 10.</td>
</tr>
</tbody>
</table>

10. An update should be initiated as soon as possible. List the expected date of completion of the update:

<table>
<thead>
<tr>
<th>10. As soon as possible.</th>
</tr>
</thead>
<tbody>
<tr>
<td>An <strong>UPDATE</strong> will be posted on the website, indicating an update is in progress.</td>
</tr>
</tbody>
</table>

11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the website. Notify the original authors of the document about this review.

<table>
<thead>
<tr>
<th>DSG Approval Date:</th>
<th>2012 Jan 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comments by DSG members:</td>
<td>I think there are two questions here and we need to ask if this should be all in one guideline or two separate ones:</td>
</tr>
<tr>
<td>1. Systemic Treatment of bone metastases - bisphosphonates and RANK ligand inhibitors. This could be an update of previous guideline.</td>
<td></td>
</tr>
<tr>
<td>2. Adjuvant treatment - this could include the data for bisphosphonates as systemic therapy of which a lot of recent data has come out. Other issue is the prevention of bone complications from AI’s (Z-FAST). This has not been covered in previous guideline and I <strong>would argue that a new guideline to address this question should be done</strong> (We have usually separated out adjuvant and metastatic disease in the past). Side effects should be covered in both questions.</td>
<td></td>
</tr>
</tbody>
</table>
DOCUMENT ASSESSMENT & REVIEW 5-STEP FLOW CHART

STEP 1: INITIATION OF THE DOCUMENT ASSESSMENT & REVIEW PROCESS

STEP 2: FIRST TELECONFERENCE TO DETERMINE:
- THE CLINICAL RELEVANCE OF THE GUIDELINE,
- IF A NEW LITERATURE SEARCH IS NEEDED, AND
- IF YES, THE SEARCH CRITERIA.

#1. Is there still a NEED for a guideline covering one or more of the topics in this document?

Yes → Archive¹

No

#2. Are all the current recommendations based on the current questions definitive* or sufficient§, and have less than 5 years elapsed since the latest search?

Yes → Endorse²

No

#3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed?

Yes → Warning³

No

#4. Do current resources allow for an updated literature search to be conducted at this time?

Yes → Deferral³

No

#5. List any new and relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered. Determine the search criteria.

Yes → New search

No

STEP 3: A NEW LITERATURE SEARCH BASED ON INPUT FROM #5 WILL BE CONDUCTED, AND THE RESULT WILL BE SENT TO THE REVIEWERS WITH A FOLLOW-UP DATE

RC emails DSG reviewer(s) the protocol

Discuss questions #1-5

Please note: No teleconference needed, IF the answers lead to one of these outcomes, PLUS the reviewer(s) complete & return the form with the answers & explanations.

Teleconference with the reviewer(s) will focus the discussion on #5: the search strategies, i.e., scope, key word(s), and inclusion and exclusion criteria

RC conducts new search

ARCHIVE

ENDORSE

WARNING

DEFERRED

NEW SEARCH

YES TO ALL

Please note:

RC conducts new search

Yes

No

No

No

Yes

No

No

Yes
STEP 4: SECOND TELECONFERENCE TO DETERMINE THE ULTIMATE STATUS OF THE DOCUMENT

#6. Are the volume and content of the newly identified evidence such that **a new document is necessary** to address the topic?

No

#7. Does the newly identified evidence **support the existing recommendations**? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?

No

#8. Does any of the newly identified evidence, on initial review, **contradict** the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?

No

#9. Is there a good reason (e.g., new, stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline?

No

#10. An update should be initiated as soon as possible. List the expected date of completion of the update.

Yes

No

Yes

Endorse

Deferral

Update

Review questions #6-9

Please note: No teleconference needed, IF the reviewer(s) complete and return the form with answers & explanations.

Teleconference with the reviewer(s) to discuss the type of update, priority, and resources.

STEP 5: FINAL OUTCOME APPROVAL; DOCUMENT ASSESSMENT & REVIEW QUESTIONS #11

#11. Circulate this form, the new evidence, and a draft document for approval by the appropriate DSG. Once approved, a copy of this form should be placed behind the cover page of the current document on the Web site. Notify the original authors of the document about this review.
DART DEFINITIONS

DART Terms

*DEFINITIVE RECOMMENDATIONS - Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

SUFFICIENT RECOMMENDATIONS - Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

WARNING - A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the website, and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

DART Outcomes

1. ARCHIVE - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, and each page is watermarked “ARCHIVED”.

2. ENDORSEMENT - An endorsed document is a document that has been reviewed by the DSG for currency and relevance, and the DSG believes it is still useful as guidance for clinical decision making. A document may be endorsed because the DSG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. DEFERRAL - A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action due to a number of reasons. The reasons for deferral should be found in the DART form and on the document.

4. UPDATE - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.