Complete Summary

GUIDELINE TITLE

The role of bisphosphonates in the management of skeletal complications for patients with multiple myeloma.

BIBLIOGRAPHIC SOURCE(S)

Hematology Disease Site Group. Imrie K, Stevens A, Makarski J, Esmail R, Meharchand J, Meyer R. The role of bisphosphonates in the management of skeletal complications for patients with multiple myeloma [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Mar 30. 21 p. (Practice guideline report; no. 6-4). [28 references]

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

**** REGULATORY ALERT ****

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

On March 25, 2005, Novartis and U.S. Food and Drug Administration (FDA) notified healthcare professionals of revisions to the DOSAGE AND ADMINISTRATION and WARNINGS sections of the prescribing information for the drug Zometa (zoledronic acid), to reflect new safety information on management of patients with advanced cancer and renal impairment, whose baseline creatinine clearance is 60 ml/min or lower. The recommended Zometa doses for patients with reduced renal function (mild and moderate renal impairment) are provided in a table. It is recommended that, during treatment, serum creatinine be measured before each dose and treatment should be withheld for renal deterioration. See the FDA Web site for more information.

Subsequently, on May 18, 2005, Novartis and the FDA notified dental healthcare professionals of revisions to the prescribing information to describe the occurrence

of osteonecrosis of the jaw (ONJ) observed in cancer patients receiving treatment with intravenous bisphosphonates, Aredia (pamidronate disodium) and Zometa (zoledronic acid). The prescribing information recommends that cancer patients receive a dental examination prior to initiating therapy with intravenous bisphosphonates (Aredia and Zometa), and avoid invasive dental procedures while receiving bisphosphonate treatment. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. See the FDA Web site for more information.

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SCOPE

DISEASE/CONDITION(S)

Skeletal complications of multiple myeloma, including lytic bone lesions, osteopenia, osteoporosis, vertebral and non-vertebral fractures, spinal cord compression, hypercalcemia, and bone pain

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Prevention
Treatment

CLINICAL SPECIALTY

Hematology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate if there is evidence that the use of bisphosphonates in patients with active multiple myeloma:

- Improves survival
- Improves quality of life
- Reduces bone pain
- Reduces or delays the development of skeletal complications

TARGET POPULATION

Adult patients with active plasma cell myeloma (symptomatic stage 1 or greater)

INTERVENTIONS AND PRACTICES CONSIDERED

Use of bisphosphonates (oral clodronate, intravenous pamidronate, or intravenous zoledronate) for prevention and treatment of skeletal complications of multiple myeloma

Note: Other bisphosphonates (etidronate, ibandronate) were considered but not recommended for use. Oral pamidronate was also not recommended.

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Vertebral and non-vertebral fractures
- Hypercalcemia
- Pain
- Gastrointestinal symptoms
- Treatment-related toxicities

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The MEDLINE (OVID) (1980 through April 2002) and CANCERLIT (OVID) (1975 through March 2002) databases were searched with the following terms: "exp Multiple Myeloma" (Medical subject heading [MeSH]), "bone metastases" (text word), "bone metasta:" (text word), and "metastatic bone disease" (text word), combined with "exp Diphosphonates" (MeSH), "exp Etidronic Acid" (MeSH), "exp Alendronate" (MeSH), "exp Clodronic Acid" (MeSH), "diphosphonate" (text word), "etidronate" (text word), "etidronate disodium" (text word), "alendronate" (text word), "clodronic acid" (text word), "clodronate" (text word), "pamidronate" (text word), "zoledronate" (text word), "ibandronate" (text word), and "bisphosphonate:" (text word). These terms were then combined with the search terms for the following study designs: practice guidelines, systematic reviews,

meta-analyses, randomized controlled trials, and controlled clinical trials. The Cochrane Library (Cochrane Database of Systematic Reviews (OVID) (2002, Issue 1), Cochrane Controlled Trials Register (OVID) (2002, Issue 1)) was also searched for systematic reviews or trials. In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/), and conference proceedings of the American Society of Clinical Oncology (ASCO) (1997 to 2001) and American Society of Hematology (ASH) (1999 to 2001) were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

The literature search was updated in September 2002: MEDLINE (OVID) (April 2002 through September 2002), CANCERLIT (OVID) (April 2002 through August 2002), Cochrane Database of Systematic Reviews (OVID) (2002, Issue 3), Cochrane Controlled Trials Register (OVID) (2002, Issue 3), and the ASCO 2002 meeting proceedings.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of any one of the following:

1. Systematic reviews or practice guidelines evaluating bisphosphonate use in patients with multiple myeloma
2. Randomized controlled trials (RCTs) or meta-analyses of RCTs comparing one bisphosphonate agent with another bisphosphonate or comparing a bisphosphonate with placebo or no treatment in patients with multiple myeloma

The trials were required to report on at least one of the following outcomes: overall survival, skeletal-related survival, quality of life, bone pain, pathological fractures (non-vertebral or vertebral), progression of bone disease (osteolytic lesions), or hypercalcemia. Treatment-related toxicity was also an outcome of interest. Many trials have evaluated endpoints assessing metabolic parameters of bone disease; while these outcomes may provide useful information establishing a "proof-of principle" for using bisphosphonates in patients with myeloma, these outcomes were not considered to be sufficient to determine recommendations for treatment.

Exclusion Criteria

1. RCTs that included patients with various types of malignancies in which the results for patients with myeloma were not reported separately
2. Phase I and II studies
3. Letter and editorials
4. Reports published in a language other than English

NUMBER OF SOURCE DOCUMENTS

Sixteen fully published reports were reviewed. One was a systematic review that included a meta-analysis, one was a practice guideline, and the other 14 reports described 12 randomized trials

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

It was decided not to pool the results of randomized controlled trials (RCTs) because of the availability of an up-to-date, published systematic review that included a meta-analysis of the available randomized controlled trials evaluating the efficacy and safety of bisphosphonates in multiple myeloma.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The members of the Disease Site Group (DSG) felt that the routine use of a bisphosphonate is recommended for patients with myeloma who have bone disease. The DSG members concluded that a number needed to treat (NNT) of 10 to prevent one patient with a vertebral fracture and a number needed to treat of 11 to prevent bone pain in one patient were clinically meaningful benefits. There was considerable discussion about the following issues:

a. **Patients without bone disease**: There was debate over the strength of the draft recommendation for using a bisphosphonate in patients without bone disease. Some members felt that a bisphosphonate should be recommended for these patients because a subset analysis of results of one trial detected benefits that were consistent with those seen in patients with bone disease and included a possible advantage in overall survival. Another view expressed was that while the use of a bisphosphonate would be reasonable and should be discussed with patients, available data were derived from a small number of patients described in a subset analysis and were insufficient to warrant "recommending" this treatment to all patients. The DSG therefore concluded that the wording of this practice guideline should be to "offer" treatment to these patients.

b. **Choice of bisphosphonate**: In the absence of compelling data detecting the superiority of one agent over others, the DSG members concluded that oral clodronate and intravenous pamidronate or zoledronate are all reasonable choices of therapy. Etidronate, oral pamidronate, and ibandronate should not be used. The DSG expressed a preference for intravenous pamidronate, as monthly intravenous infusions were perceived to be better tolerated, but unlike the American Society of Clinical Oncology (ASCO) expert panel, did not feel that the evidence clearly favoured pamidronate or zoledronate over clodronate.
c. **Duration of therapy**: Both the clodronate and pamidronate trials suggest that a prolonged duration of therapy (at least 24 months) is beneficial. Given the mechanism of action of bisphosphonates, the DSG felt it was reasonable to continue treatment until the myeloma becomes refractory to therapy. At this point, there may still be benefits in providing treatment with a bisphosphonate in order to palliate pain associated with progressive bone disease.
d. **Autologous stem cell transplantation**: Although no trials were performed specifically in patients undergoing autologous stem cell transplantation, DSG members concluded that it was reasonable to generalize recommendations to this setting.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 115 practitioners in Ontario (58 medical oncologists and 57 hematologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on June 26, 2003. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Hematology Disease Site Group (DSG) reviewed the results of the survey.

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Nine of 13 members of the PGCC returned ballots. One member did not review the report for approval as this individual is a member of the Hematology DSG.

Five PGCC members approved the practice guideline report as written, two members approved the guideline and provided suggestions for consideration by the Hematology DSG, and one member approved the guideline conditional on the Hematology DSG addressing specific concerns.

No changes were made to the guideline in response to the comments made by the PGCC.

The practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Hematology DSG and has been approved by the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- It is recommended that all patients with myeloma who have lytic bone lesions, osteopenia, or osteoporosis receive a bisphosphonate.
- For patients with myeloma who do not have lytic bone lesions, osteopenia, or osteoporosis, health care providers should inform patients of the potential benefits and risks of therapy and offer treatment with a bisphosphonate to these patients.
- Evidence exists to support the use of clodronate (800 mg orally twice daily), pamidronate (90 mg intravenously every four weeks), or zoledronate (4 mg intravenously every four weeks). Patient preference, tolerance, and convenience will influence the choice of agent. Patients who are unable to tolerate the initial agent should be offered an alternative agent.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials and meta-analyses.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- In the systematic review, 11 trials that included 2,183 patients compared the use of a bisphosphonate with placebo or no treatment. Outcomes assessed included overall survival, vertebral and non-vertebral fractures, hypercalcemia, pain, and gastrointestinal

symptoms. Of these outcomes, vertebral fractures (Peto odds ratio 0.59; 95% confidence interval 0.45 to 0.78; p = 0.0001) and pain (Peto odds ratio 0.59; 95% confidence interval 0.46 to 0.76; p = 0.00005) were significantly reduced in patients receiving bisphosphonates. These results translate to a number-needed-to-treat value of 10 (95% confidence interval 7 to 20) in order to avoid one patient with a vertebral body fracture and 11 (95% confidence interval 7 to 28) in order to avoid pain in one patient. The authors of the review suggest that clodronate and pamidronate might be the preferred agents.
- In a randomized trial comparing intravenous zoledronate with intravenous pamidronate in 510 patients with multiple myeloma and 1,130 patients with breast cancer, no significant differences were detected in overall or progression-free survival, total or specific skeletal events, incidence of pain or analgesic use, or treatment-related toxicities.

POTENTIAL HARMS

- Gastrointestinal symptoms (grade III/IV) were the most commonly reported adverse effects in all trials.
- Renal function is an important consideration when using a bisphosphonate to treat patients with myeloma. Clodronate, pamidronate, and zoledronate are excreted unchanged by the kidneys, and nephrotoxicity has been reported with each of these agents.

CONTRAINDICATIONS

CONTRAINDICATIONS

Clodronate is contraindicated in patients with a serum creatinine value greater than 440 micromoles/L. Limited experience exists with pamidronate and zoledronate in patients with severe renal impairment; these agents may be used with careful monitoring of renal function.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Twenty-four hour urinary protein levels and serum creatinine values should be monitored in patients with myeloma who are receiving a bisphosphonate. Patients with new unexplained albuminuria or an increasing serum creatinine should have the bisphosphonate withheld pending additional evaluation. Reintroduction of bisphosphonate therapy at a slower infusion rate (for intravenous formulations) can be considered for patients demonstrating resolution of the progressive albuminuria or increasing serum creatinine.
- Clodronate is contraindicated in patients with a serum creatinine value greater than 440 micromoles/L. Limited experience exists with pamidronate and zoledronate in patients with severe renal

impairment; these agents may be used with careful monitoring of renal function.
- No dose modification of pamidronate or zoledronate is required for patients with renal dysfunction.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Hematology Disease Site Group. Imrie K, Stevens A, Makarski J, Esmail R, Meharchand J, Meyer R. The role of bisphosphonates in the management of skeletal complications for patients with multiple myeloma [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Mar 30. 21 p. (Practice guideline report; no. 6-4). [28 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Mar 30

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Hematology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Hematology Disease Site Group (DSG) disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The role of bisphosphonates in the management of skeletal complications for patients with multiple myeloma. Summary. Toronto (ON): Cancer Care Ontario (CCO). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on June 30, 2004. The information was verified by the guideline developer on July 19, 2004. This summary was updated by ECRI on May 20, 2005, following the U.S. Food and Drug Administration advisory on Aredia (pamidronate disodium) and Zometa (zoledronic acid).

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