



Evidence-based Series 6-4: EDUCATION AND INFORMATION 2015

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

The Role of Bisphosphonates in the Management of Skeletal Complications for Patients with Multiple Myeloma

Members of the Hematology Disease Site Group

An assessment conducted in October 2015 put This Evidence-based Series (EBS) 6-4 in the Education and Information Section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardize process to ensure the currency of each document ([PEBC Assessment & Review Protocol](#))

The reviewed EBS report consists of 4 sections
and is available on the [CCO Web site](#) on the PEBC [Hematology DSG page](#)
Section 1: Clinical Practice Guideline
Section 2: Systematic Review
Section 3: Guideline Development and External Review
Section 4: Guideline Review Summary

Release Date: October 30, 2012

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Complications for Patients with Multiple Myeloma**

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version Mar 2004	1980-2003	Full Report	Web publication Peer reviewed publication ¹	NA
Update Mar 2007	2003-2006	Full Report	Web publication	NA
Reviewed Oct 2012	2006-2012	New data found in Section 4: Document Summary & Review Tool	Updated Web publication	2007 recommendations require an UPDATE

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¹ Imrie K, Stevens A, Makarski J, Esmail R, Meharchand J, Meyer RM, et al. Role of bisphosphonates in the management of skeletal complications in patients with multiple myeloma. Curr Oncol. 2005;12(1):3-17.

Evidence-based Series 6-4: TO BE UPDATED

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

**The Role of Bisphosphonates in the Management of Skeletal
Complications for Patients with Multiple Myeloma:
A Clinical Practice Guideline**

*K. Imrie, A. Stevens, J. Makarski, R. Esmail, J. Meharchand, R. Meyer,
and the members of the Hematology Disease Site Group*

Original Report Date: March 30, 2004

Current Report Date: March 12, 2007

The 2007 guideline recommendations require an

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*

Questions

For patients with active multiple myeloma, is there evidence that the use of bisphosphonates:

1. Improves survival?
2. Improves quality of life?
3. Reduces bone pain?
4. Reduces or delays the development of skeletal complications?

For patients with multiple myeloma who receive treatment with a bisphosphonate:

5. What is the association of bisphosphonates with osteonecrosis of the jaw (ONJ)?
6. How can this complication be prevented and managed?

Target Population

These recommendations apply to adult patients with active plasma cell myeloma (symptomatic stage 1 or greater).

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 lesions, osteopenia, or osteoporosis, health care providers should inform patients of the potential benefits and risks of therapy and offer treatment with a bisphosphonate.
- Evidence exists to support the use of clodronate (800 mg orally twice daily), pamidronate (90mg 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 a alternative agent.
- It is recommended that patients be treated for a minimum of two years.
- After two years of bisphosphonate treatment:
 - Patients who have achieved remission and are in stable plateau phase off treatment, should consider discontinuing the use of bisphosphonates.
 - Patients who still require active treatment for their myeloma, should continue on bisphosphonates, but may consider having the frequency decreased to every three months if on pamidronate or zoledronate.
- Patients whose myeloma becomes active following an initial response should resume monthly bisphosphonate therapy while on active treatment.
- Patients receiving bisphosphonates should have comprehensive dental evaluation before or soon after starting bisphosphonate treatment and undergo invasive dental procedures, if needed, before starting bisphosphonate treatment.
- Patients should be followed by dentistry and should be made aware of the importance of oral hygiene and of the early signs of ONJ.

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 $\mu\text{mol/L}$. 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.

Key Evidence

- One systematic review with a published-data meta-analysis, one practice guideline, and reports of 12 randomized controlled trials form the basis of evidence for this practice guideline report. Eleven of the 12 trials identified were included in the systematic review.
- 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.
- No randomized trials addressing osteonecrosis of the jaw in patients receiving bisphosphonates were identified. Two consensus statement documents and eight case series addressing this complication were included in this evidence-based series.

Related Guideline

Practice Guidelines Initiative Practice Guideline Report #1-11: *Use of Bisphosphonates in Patients with Bone Metastases from Breast Cancer.*

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

**The Role of Bisphosphonates in the Management of Skeletal
Complications for Patients with Multiple Myeloma:
A Systematic Review**

*K. Imrie, A. Stevens, J. Makarski, R. Esmail, J. Meharchand, R. Meyer,
and the members of the Hematology Disease Site Group*

Original Report Date: March 30, 2004

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QUESTIONS

For patients with active multiple myeloma, is there evidence that the use of bisphosphonates:

1. Improves survival?
2. Improves quality of life?
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For patients with multiple myeloma who receive treatment with a bisphosphonate:

5. What is the association of bisphosphonates with osteonecrosis of the jaw?
6. How can this complication be prevented and managed?

INTRODUCTION

Skeletal complications are common in myeloma and are a major source of morbidity. Complications include osteopenia, osteolytic lesions, vertebral and non-vertebral fractures, spinal cord compression, and hypercalcemia (1). Skeletal lesions can cause pain, deformity, and neurologic impairment and may require use of analgesic medications, local radiation therapy, and orthopedic or neurosurgical interventions. In patients with myeloma, chemotherapy is effective at palliating symptoms and prolonging survival but does not prevent ultimate development of bone complications (2). Bisphosphonates are potent inhibitors of osteoclastic activity and are widely used to treat hypercalcemia and pain associated with malignancies that

involve bone (3). The role of bisphosphonates in preventing bone resorption provides a rationale for use to delay or prevent progressive bone disease in patients with myeloma.

In 1996, the Hematology Disease Site Group (Hematology DSG) determined that a practice guideline report assessing bisphosphonate use for patients with myeloma was a high priority. Emerging data reporting potential effectiveness for using bisphosphonates in patients with myeloma and a perception of variation in practices across Ontario influenced this decision. In addition, it was recognized that the acquisition costs of bisphosphonate agents were substantial and could present barriers to utilization. The Hematology DSG approved a draft practice guideline report in 1997. A presentation of this report was made to the Cancer Care Ontario Policy Advisory Committee (PAC), which contributed to a PAC decision to recommend funding of pamidronate for patients with advanced-stage myeloma and bone disease. A draft practice guideline report was disseminated for external review by Ontario practitioners in 1999 and received a high level of support. However, because of the continuous availability of new evidence necessitating an ongoing updating process, a final version of this guideline was not completed. Beginning in 2002, the Hematology DSG determined that important new data were available and that this evidence was sufficiently stable to permit a process to update recommendations and complete the guideline process. This updated report includes recent reports of randomized trials and a Cochrane systematic review by Djulbegovic et al. (4) and incorporates conclusions reached from a similar guideline process completed by a committee sponsored by the American Society of Oncology (ASCO) (5). This practice guideline report was resubmitted to Ontario practitioners for external review.

In 2006, the Hematology DSG revised the practice guideline to include a systematic review of the association of bisphosphonate therapy with osteonecrosis of the jaw, in response to emerging evidence linking this complication to bisphosphonate treatment.

METHODS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC) using the methods of the Practice Guidelines Development Cycle (7). Evidence was selected and reviewed by one member of the Hematology DSG and a methodologist. Members of the Hematology DSG disclosed potential conflict of interest information.

This systematic review is a convenient and up-to-date source of the best available evidence on bisphosphonates in multiple myeloma, 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 PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

BISPHOSPHONATE THERAPY

Literature Search Strategy

The MEDLINE (OVID) (1980 through December 2006) 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) (2006, Issue 4), Cochrane Controlled Trials Register (OVID) (2006, Issue 4)) 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 2006) and American Society of Hematology (ASH) (1999 to 2006) 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 and the authors' personal files.

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.

Synthesizing the Evidence

It was decided not to pool the results of RCTs because of the availability of an up-to-date, published systematic review that included a meta-analysis of the available RCTs evaluating the efficacy and safety of bisphosphonates in multiple myeloma (4).

OSTEONECROSIS OF THE JAW

In December 2006, in response to emerging evidence on osteonecrosis of the jaw (ONJ), a potential complication of bisphosphonate therapy, a separate search of the literature was conducted in order to evaluate this toxicity.

Literature Search Strategy

The MEDLINE (1980 to December 21, 2006) and Cochrane Library (2006, Issue 4) databases were searched with the following terms: diphosphonates (MeSH and text word [tw]), bisphosphonates (tw), etidronate (tw), alendronate (tw), clodronate (tw), pamidronate (tw), zoledronate (tw), and ibandronate (tw) were combined with search terms for osteonecrosis

(MeSH and tw). In addition, the conference proceedings of the ASH (2002-2006) and ASCO (2003-2006) were hand searched.

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 that reported on the incidence or risk factors for development of ONJ:

1. Systematic reviews, meta-analyses, or practice guidelines evaluating the use of bisphosphonates 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.
3. Case series of patients with multiple myeloma who receive treatment with a bisphosphonate.

Exclusion Criteria

1. Studies that included patients with various types of malignancies in which the results for patients with myeloma were not reported separately.
2. Reports published in a language other than English.

RESULTS

BISPHOSPHONATE THERAPY

Literature Search Results

A total of 640 citations were retrieved from the MEDLINE and Cochrane Library searches. No additional citations were identified from the CANCERLIT database. After applying the eligibility criteria to the citations, 19 fully published reports met the inclusion criteria for this systematic review. One additional fully published report was identified in the personal files of one author after an earlier abstract publication of that report was identified through a reference list search. In total 20 fully published reports were identified, of which one was a systematic review that included a meta-analysis (4), two were practice guideline reports (5,6), and the remaining 17 reports described 14 randomized trials (8-24) (Table 1). Eleven (8-10,12-14,17-19,21,25) of the 14 trials were included in the published systematic review (4); the systematic review included a total of 11 trials (Table 2), of which one (25) is the earlier abstract of a full report (24) found in our search.

Table 1. Randomized controlled trials included in this practice guideline report.

Bisphosphonate and comparison evaluated	Number of trials	Number of papers	First author, year (reference)
Etidronate vs placebo	2	2	Daragon, 1993 (8) Belch, 1991 (9)
Clodronate vs placebo or no treatment	4	5	McCloskey, 2001 (10) (McCloskey, 1998) (11) Heim, 1995 (12) Lahtinen, 1992 (13) Delmas, 1982 (14)
Pamidronate vs placebo or no treatment	6	7	Attal, 2006 (15) Musto, 2003 (16) Kraj, 2000 (17) Terpos, 2000 (18) Berenson, 1998 (19) (Berenson, 1996) (20)

			Brincker, 1998 (21)
Zoledronate vs pamidronate	1	2	Rosen, 2001 (22) (Rosen, 2003) (23)
Ibandronate vs placebo	1	1	Menssen, 2002 (24)

Note: vs.=versus.

Systematic Review and Meta-analysis

In a systematic review published in 2002, Djulbegovic et al. (4) analyzed the effect of bisphosphonate use on morbidity and mortality of patients with multiple myeloma. The major outcomes of interest evaluated were the number- or time-to-specific or composite skeletal events (e.g., pathological fractures) and overall survival. Secondary outcomes included pain, incidence of hypercalcemia, and treatment-related toxicities. This review included a published data meta-analysis of RCTs comparing a bisphosphonate with placebo or no treatment. Bisphosphonates were any of etidronate, clodronate, pamidronate, or ibandronate. The literature search was comprehensive and identified 123 articles from which 11 RCTs met the eligibility criteria (Table 2). The authors also obtained additional data for one of the trials (25) directly from the manufacturer of the bisphosphonate and from the author of this published abstract. Two independent reviewers used the Jadad (26) five-point scale to assess the methodological quality of these 11 trials.

The 11 trials included 1,113 patients in the treatment arms and 1,070 patients in the control arms. Results describing quality of life, progression-free survival, skeletal-related mortality, and bone density were not sufficiently or consistently reported among these 11 trials to permit pooling of data. Among the possible treatment-related toxicities, only gastrointestinal symptoms were sufficiently described to permit pooling of data. Meta-analyses were therefore performed using evaluable data for the outcomes of mortality, vertebral and non-vertebral fractures, hypercalcemia, pain, and gastrointestinal toxicity (Table 3). These meta-analyses were performed using Review Manager (Metaview © Update Software) (27). Heterogeneity was tested with both the fixed and random effects models. All results were analyzed using the Peto odds ratio (OR) (reported with 95% confidence intervals [CI]), and some outcomes were also analyzed using absolute risk reductions with reporting of a number needed to treat (NNT).

Table 2. Randomized controlled trials included in the systematic review by Djulbegovic et al. 2002.

Bisphosphonate evaluated	Number of articles	First author, year (reference)	Jadad Scale score
Etidronate	2	Daragon, 1993 (8) Belch, 1991 (9)	4 5
Clodronate	4	McCloskey, 2001 (10) Heim, 1995 (12) Lahtinen, 1992 (13) Delmas, 1982 (14)	4 3 4 3
Pamidronate	4	Kraj, 2000 (17) ^a Terpos, 2000 (18) Berenson, 1998 (19) Brincker, 1998 (21)	1 3 5 5
Ibandronate	1	Fontana, 1998 (abstract) (25) ^b	5

^aduplicate of this article (Kraj M, Poglod R, Pawlikowsky J, Maj S. The effect of long-term pamidronate treatment on skeletal morbidity in advanced multiple myeloma. Acta Haematologica Polonica 2000;31:379-89) exists and was identified in Djulbegovic et al. 2002 (4).

^bdata for this trial were obtained directly from the manufacturer and from the abstract's author.

Table 3. Results of the Djulbegovic et al. 2002 meta-analysis.

Outcome (number of trials included)	Bisphosphonate vs control (number of patients)		Peto OR (95% CI)	p value
	Patients evaluated ^a	Results ^a		
Mortality (10)	1,079 vs 1,048	557 vs 549	0.99 (0.88 to 1.12)	0.9
Vertebral fractures (7)	575 vs 541	141 vs 188	0.59 (0.45 to 0.78)	0.0001
Non-vertebral fractures (6)	708 vs 681	102 vs 93	1.05 ^b (0.77 to 1.44)	0.7
Hypercalcemia (8)	1,044 vs 1,002	84 vs 101	0.76 (0.56 to 1.03)	0.07
Pain ^c (8)	657 vs 624	276 vs 318	0.59 (0.46 to 0.76)	0.00005
Gastrointestinal symptoms ^d (6)	853 vs 836	110 vs 86	1.28 (0.95 to 1.74)	0.11

Note: OR=odds ratio, CI=confidence interval.

^aevaluable patient data.

^bheterogeneity: chi square 9.6, df=4, p=0.048.

^creporting of pain was not uniform across trials; the number of patients who reported pain was pooled.

^dgastrointestinal symptoms (grade III/IV) were the most commonly reported adverse events in all trials; however, because the manner by which specific symptoms were reported varied among trials, all gastrointestinal symptoms were pooled.

From their systematic review and meta-analyses, Djulbegovic et al. concluded that there was evidence to support using a bisphosphonate to reduce vertebral fractures. Additional evidence identified that use of a bisphosphonate was associated with a reduction in pain, but the authors commented that there was less confidence in this conclusion because data had been reported in an inconsistent manner across studies. The meta-analysis results translate to a NNT of 10 (95% CI, 7 to 20) in order to avoid one patient with a vertebral body fracture and a NNT of 11 (95% CI, 7 to 28) in order to avoid pain in one patient. The authors suggested that clodronate and pamidronate might be the preferred agents among the bisphosphonates reviewed.

Practice Guideline Results

American Society of Clinical Oncology

ASCO has published a practice guideline evaluating the role of bisphosphonates in patients with myeloma with specific attention to the role of these agents in preventing and treating bone disease (5). This guideline addressed several components of bisphosphonate use and reached the following conclusions (with the level of evidence supporting each conclusion indicated in brackets):

- i) use of a bisphosphonate is recommended for patients with myeloma who have lytic bone disease (data from RCTs and a meta-analysis);
- ii) patients with myeloma treated with a bisphosphonate should have an evaluation of 24-hour urine protein excretion and serum creatinine every three to six months. The drug should be discontinued if albuminuria of more than 500 mg in 24 hours, or an increase in the serum creatinine of 0.5 mg/dL, or an absolute serum creatinine value of more than 1.4 mg/dL (123 µmol/litre) among patients with normal baseline serum creatinine levels is observed. The drug may be re-instituted if the renal problems resolve; a longer infusion time should then be considered (data from case series);

- iii) a bisphosphonate should be continued until there is a general decline in the patient's performance status necessitating an assessment of the balance between the benefits and the inconvenience of continued therapy (panel consensus);
- iv) myeloma patients with osteopenia as the sole marker of bone disease should be treated with a bisphosphonate (panel consensus);
- v) patients with a solitary plasmacytoma, smouldering myeloma, or a monoclonal gammopathy of undetermined significance as their sole indication for therapy should not be treated with a bisphosphonate (panel consensus);
- vi) monitoring of biochemical markers of bone disease is not required for patients being treated with a bisphosphonate (panel consensus); and,
- vii) myeloma patients experiencing bone pain should receive a bisphosphonate (data from randomized trials).

The guideline panel recommended that when a bisphosphonate is used, intravenous pamidronate or zoledronate are the drugs of choice. The panel concluded that data supporting the use of oral clodronate were less compelling because clodronate had not yet been approved for use in the United States (US), there were methodological issues in the studies evaluating clodronate that might result in an over-estimation of benefits (due to use of events per year rather than a time-to-event analysis), there was incomplete follow-up in one of the studies evaluating clodronate, and the studies did not combine multiple outcome measures into an aggregate endpoint. The publication states that the panel did not reach unanimous consensus on the interpretation of the clodronate data obtained from the published meta-analysis.

Mayo Clinic consensus statement

The Mayo Clinic published a consensus statement on the use of bisphosphonates in multiple myeloma in 2006 (6). The consensus statement document did not include a systematic review of the literature. However, the authors stated that they used the same methodology that was used to develop the ASCO guidelines (5) and they provided a grading of the evidence and the level of recommendations. The recommendations (6) of the Mayo Clinic Myeloma Group specific to the treatment of skeletal-related complications are:

Multiple myeloma and lytic bone disease:

- Intravenous bisphosphonates should be administered monthly for patients with multiple myeloma and lytic bone disease on plain radiographs.

Multiple myeloma with osteopenia or osteoporosis, but without lytic bone disease:

- Bisphosphonates are a reasonable treatment option for patients with multiple myeloma, who do not have lytic bone disease, and for whom osteopenia or osteoporosis is evident on bone mineral density studies.

Smouldering multiple myeloma:

- Bisphosphonates are not recommended for the treatment of patients with smouldering multiple myeloma. Patient with smouldering multiple myeloma should only receive treatment with bisphosphonates as part of a clinical trial.

Duration of bisphosphonate therapy:

- Patients should receive monthly infusions of bisphosphonates for two years.
- After two years, if the patient has achieved remission and is in stable plateau phase off treatment, the bisphosphonates can be discontinued.
- After two years, if patients still require active treatment, the frequency of bisphosphonate infusions can be decreased to every three months.

Choice of bisphosphonate:

- In patients with newly diagnosed myeloma, we favour the use of pamidronate over zoledronic acid.

The authors also provided recommendations regarding the prevention and treatment of ONJ. Those recommendations are detailed in the *Osteonecrosis of the Jaw* section of this systematic review.

Randomized Controlled Trials

In addition to the systematic review by Djulbegovic et al. and the ASCO practice guideline, the literature search by the Hematology DSG identified 17 articles describing 14 RCTs (8-24). Eleven of these trials (8-10,12-14,17-19,21, 25) were included in the Djulbegovic et al. systematic review. A trial reported by Rosen (22), and updated by Rosen (23) in 2003, that compared zoledronate with pamidronate was not included in the systematic review, presumably because the trial compared bisphosphonate agents rather than a bisphosphonate with placebo or no treatment. In addition, since the reporting of the systematic review, the trial comparing ibandronate with placebo (25) has been published in article form (24).

Randomized trials comparing a bisphosphonate with placebo or no treatment

Thirteen RCTs were identified in this category; details of trial methodology are summarized in Table 4, and results are summarized in Table 5. Based on the methodological strength and the significance of trial results, four trials are discussed in detail in the text below, and eight trials are briefly summarized.

Table 4. Randomized controlled trials included in this practice guideline report: methods.

Study (reference)	Drug/Route of administration	Placebo / Blinding	Number evaluated	New diagnosis vs previous therapy	Type of chemotherapy ^a
Daragon 1993 (8)	Etidronate (10 mg/kg/d for 4 mo)/ Oral	Placebo/ Double blind	78	New	Cyclophosphamide + prednisone
Belch 1991 (9)	Etidronate (5 mg/kg/d) ^b / Oral	Placebo/ Double blind	166	New	Melphalan + prednisone
McCloskey 2001, 1998 (10, 11)	Clodronate (1600 mg/d) ^c / Oral	Placebo/ Double blind	536	New	Multiple regimens
Heim 1995 (12)	Clodronate (1600 mg/d for 1 y)/ Oral	No placebo/ Not blinded	157	New	Melphalan + prednisone
Lahtinen 1992 (13)	Clodronate (2.4 g/d for 24 mo) ^d / Oral	Placebo/ Double blind	350	New	Melphalan + prednisone
Delmas 1982 (14)	Clodronate (1600 mg/d planned for 2y)/ oral	Placebo/ Double blind	13	Previously treated	Multiple regimens
Attal 2006 (15)	Pamidronate (90 mg every 4 wk) ^e intravenous ^f	Not reported	597	New	VAD + double ASCT
Musto 2003 (16)	Pamidronate (60 mg monthly) intravenous	No placebo/ Not blinded	90	New	Not reported
Kraj 2000 (17)	Pamidronate (60 mg monthly)/	No placebo/ Not blinded	46	Unknown	VMCP/VBAP

	intravenous				
Terpos 2000 (18)	Pamidronate (90 mg, monthly)/ intravenous	No placebo/ Not blinded	62	New	Multiple regimens
Berenson 1998 (19)	Pamidronate (90 mg every 4 wk for 21 mo)/ intravenous	Placebo/ Double blind	392	New and previously treated	Not defined
Brincker 1998 (21)	Pamidronate (300 mg/d) ^g / oral	Placebo/ Double blind	304	New and previously treated	Melphalan + prednisone +/- interferon
Menssen 2002 (24)	Ibandronate (2 mg/mo for 12 to 24 mo)/ intravenous	Placebo/ Double blind	392	New and previously treated	Not defined

Note: ASCT=autologous stem cell transplantation; d=day; mo=month; VAD=vincristine, doxorubicin, dexamethasone; VBAP=vincristine, carmustine, Adriamycin, prednisone; VMCP=vincristine, melphalan, cyclophosphamide, prednisone; y=year.

^aChemotherapy information listed in this column applies to both randomized arms in the trials.

^bFrom randomization until death or discontinuation due to intolerance or refusal.

^cContinued indefinitely or until evidence of progressive osteolytic lesions or of hypercalcemia unresponsive to high fluid intake and cytotoxic chemotherapy.

^dAdministered starting at 4 weeks after first course of chemotherapy.

^eAdministered starting 2 months after second ASCT.

^fTwo study arms received pamidronate: one received pamidronate alone, the second received pamidronate and thalidomide (400 mg orally with a dose reduction to a minimum of 50 mg for treatment-related toxicity).

^gUntil the end of study, discontinuation from the trial, or death.

Table 5. Randomized controlled trials included in this practice guideline report: results.

Study (reference), drug	Outcomes evaluated	Outcome assessment	Results
Daragon 1993 (8), etidronate	Survival	Time to event	NS
	Pain	Events per unit of time (analgesic use)	NS
	Lytic lesions	Events per unit time	NS
	Fractures	Events	NS
	Hypercalcemia	Events per unit time	NS
Belch 1991 (9), etidronate	Survival	Time to event	At 4y: Etidronate 14.5% vs Placebo 44.5%; p=0.02
	Pain	Events	NS
	Bone progression-free survival	Time to event	NS
	Fractures	Events	NS
	Hypercalcemia	Events	NS
McCloskey 1998 (11), 2001 (10), clodronate	Survival	Time to event	NS
	Back pain	Events per unit time	At 24 mo: Clodronate 10.9% vs Placebo 19.9%; p<0.05
	Bone pain: ribs and upper and lower limbs	Events per unit time	NS
	Vertebral fractures	Events	Patients with fracture: Clodronate 38% vs Placebo 55%; p=0.012
	Non-vertebral fractures	Events	Patients with fracture: Clodronate 6.8% vs Placebo 13.2%; p=0.036
	Hypercalcemia	Events	NS
Heim 1995 (12), clodronate	Pain	Events per unit time ^a	At 9 mo: Clodronate 13% vs Placebo 44%; p=0.10 ^b (NS)
	Osteolytic lesion	Events per unit time	NS
	Fractures	Events	NS

	Hypercalcemia	Events	NS
Lahtinen 1992 (13), clodronate	Survival	Events per unit time	NS
	Pain	Events per unit time	NS
	Osteolytic lesion	Events per unit time	At 24 mo among those who had radiographs: Clodronate 12% vs Placebo 24%; p=0.026
	Vertebral fractures	Events per unit time (data not clearly indicated; extracted from Cochrane review)	NS
	Non-vertebral fractures	Events per unit time	NS
	Hypercalcemia	Events	NS
Delmas 1982 (14), clodronate	Survival	Events	NS
	Pain	Events per unit time	NS
	Osteolytic lesion	Events per unit time	NS
	Vertebral fractures	Events per unit time	NS
	Non-vertebral fractures	Events per unit time	NS
	Hypercalcemia	Events	NS
Attal 2006 (15) pamidronate	Survival	Overall (time to event) Event-free (time to event; randomization to progression, relapse, or death) Relapse-free (time to event; date of minimal response to progression) Skeletal event-free (time to event; randomization to first skeletal event)	Pamidronate alone vs Untreated: 4-year, 74% vs 77%, p=0.7 Pamidronate alone vs Untreated: 3-year, 37% vs 36%, p=0.6 Pamidronate alone vs Untreated: 3-year, 39% vs 38%, p=0.7 Pamidronate alone vs Untreated: 3-year, 66% vs 63%, p=NS
	Number of skeletal events	Events at progression	Pamidronate alone vs Untreated: 21% vs 24%, p=NS
	Survival	Time to event (progression)	NS
	Pain	NR	NR
	Osteolytic lesion	Events at progression	Pamidronate vs Untreated: Single lesion: 20% vs 36%; p=NR Multiple lesions: 10% vs 36%; p=NR
Musto 2003 (16), pamidronate	Number of skeletal events	Events at progression	Pamidronate 40% vs Untreated 82%; p<0.01
	Hypercalcemia	Events at progression	Pamidronate 10% vs Untreated 27%; p=NR
	Survival	Not indicated; data extracted from Cochrane review	NS
	Pain	Combined scale assessments of pain score, analgesic consumption, and performance status	Mean change in score from baseline: Pamidronate 4.29 ^c vs Untreated 7.78 ^c ; p<0.05
	Osteolytic lesion	Events per unit time	NS
Kraj 2000 (17), pamidronate	Number of skeletal events	Events per unit time	Mean skeletal events/y: Pamidronate 1.82 vs Untreated 2.72; p=0.013
	Hypercalcemia	Events	NS
	Survival	Not indicated; data extracted from Cochrane review	NS
	Pain	Events per unit time ^d	Mean score at 14 mo: Pamidronate 3.99 vs Untreated 0.8; p<0.01
	Lytic lesions	Events	NS
Terpos 2000 (18), pamidronate	Vertebral fractures	Events	NS

	Hypercalcemia	Not indicated; data extracted from Cochrane review	NS
Berenson 1998 (19), pamidronate	Survival	Time to event	NS
	Pain	Events	Pamidronate 61% vs Placebo 71%; p<0.05
	Any skeletal event	Time to event (after 21 cycles)	Pamidronate 50% vs Placebo 58%; p=0.016
	Lytic lesions	Events	NS
	Vertebral fractures	Time to event (after 21 cycles)	Pamidronate 23% vs Placebo 36%; p = 0.007
	Hypercalcemia	Time to event (after 21 cycles)	NS

Brincker 1998 (21), pamidronate	Survival	Time to event	NS
	Pain	Events per unit time (severe pain)	Mean events/y: Pamidronate 0.58 vs Placebo 0.8; p=0.04
		Intensity (self-assessment score)	NS
		Amount of analgesics	NS
	Any skeletal event	Time to event	NS
	Lytic lesions	Events per unit time	NS
	Non-vertebral fractures	Events per unit time	NS
	Vertebral fractures	Events per unit time	NS
	Hypercalcemia	Events per unit time	NS
Menssen 2002 (24), ibandronate	Survival	Time to event	NS
	Pain	Pain score (ordinal scale)	NS
	Any skeletal event	Time to event	NS
	Lytic lesions	Events	NS
	Vertebral fractures	Events per unit time	NS
	Non-vertebral fractures	Events per unit time	NS
	Hypercalcemia	Events per unit time	NS

Note: mo=month, NS=not statistically significant, vs=versus, y=year.

^aCalculated from patients reporting no pain or no need of treatment.

^bAnalyzed as a difference in proportions (http://department.obg.cuhk.edu.hk/ResearchSupport/Independent_2x2_table.ASP)

^cData estimated from end of curve provided in paper.

^dEvaluation of pain: modification of dose and duration of analgesic and anti-inflammatory treatment and days off work, in bed, and hospitalized because of pain.

Etidronate

Etidronate has been evaluated in two RCTs (8,9); in both trials, the drug was given orally and compared with a placebo. Both trials were included in the published systematic review. Among the outcomes of interest, no benefits were observed in patients randomized to receive a bisphosphonate. Of concern was the observation in one trial (9) that survival at four years was superior in patients allocated to receive placebo (45% versus [vs.] 15%; p=0.02). An identifiable cause for this difference was not determined.

Clodronate

Clodronate has been evaluated in four RCTs that have been reported in five publications (10-14). In all trials, clodronate was given orally and compared with either placebo (10,11,13,14) or no treatment (12). All four trials were included in the published systematic review.

Less weight was given to two trials (12,14) that had important methodological limitations. In the trial reported by Heim et al. (12), patients in the control group did not receive a placebo and, therefore, patients and health care providers were not blinded to treatment allocation. In addition, the primary analysis of this trial was done by considering three subgroups that were each defined by the duration of follow-up from randomization; a primary analysis of all randomized patients by intention to treat was not completed. The trial reported by Delmas et al.

(14) included only 13 patients and therefore has insufficient statistical power to detect important clinical differences.

Two other trials testing clodronate are described in greater detail. McCloskey et al. has reported the initial (11) and longer-term (10) results of the VI Medical Research Council Myelomatosis Trial. In this double-blind trial, previously untreated patients were randomized to receive oral clodronate 1600 mg per day or placebo; 536 eligible patients were evaluated. Patients were not required to have pre-existing bone disease in order to be eligible for the study. Multiple chemotherapy regimens were included as part of standard therapy. Outcomes of interest for this guideline review included overall survival, reporting of pain, and the number of patients experiencing vertebral or non-vertebral fractures and hypercalcemia. No difference in overall survival between groups was detected. Patients randomized to receive clodronate had fewer vertebral (38% vs. 55%; $p=0.012$) and non-vertebral fractures (6.8% vs. 13.2%; $p=0.036$), and at 24 months, were less likely to report ongoing problems with back pain (10.9% vs. 19.9%; $p<0.05$). No difference in the incidence of hypercalcemia was detected. In subset analyses of patients without evidence of a vertebral fracture at the time of randomization, fewer fractures were seen in patients randomized to receive clodronate (29.8 vs. 49.6 per 100 patient years; $p<0.02$) (11), and in patients without evidence of any fracture at randomization, median overall survival was reported to be longer in patients receiving clodronate (59 vs. 37 months; $p=0.004$) (10).

Lahtinen et al. (13) has reported the results of a double-blind trial in which 350 previously untreated patients were randomized to receive either oral clodronate (2.4 g per day) or placebo for 24 months. Chemotherapy consisted of melphalan and prednisone. Outcomes assessed included overall survival, development of new osteolytic bone lesions, vertebral and non-vertebral fractures, hypercalcemia, and pain as reported using a four-point scale. Hypercalcemia was analyzed as the number of patients experiencing hypercalcemia at any time; all other outcomes were analyzed as the number of patients with an event per unit time. Among these outcomes, a significant difference was detected for only the development of new osteolytic bone lesions: patients randomized to receive clodronate were less likely to develop new lesions (12% vs. 24%; $p=0.026$) than were patients allocated to placebo.

Pamidronate

Pamidronate has been evaluated in six RCTs that have been reported in seven publications (15-21). In five trials, pamidronate was given intravenously (15-20), and in one trial, the drug was given orally (21). Four of the six trials were included in the published systematic review (17-21).

Less weight was given to four trials (16-18,21) that had important methodological limitations. The trials reported by Musto *et al.* (16), Kraj *et al.* (17) and Terpos *et al.* (18) did not include use of a placebo in the control group and were thus not blinded, and all had relatively small sample sizes of 90, 46, and 62 patients, respectively. The study reported by Brincker *et al.* (21) tested the use of oral pamidronate and did not detect a difference between the randomized groups in the incidence of any skeletal event.

The study reported by Attal *et al.* (15) treated 780 patients with MM, who were less than 65 years of age, and who were previously untreated with a regimen consisting of vincristine, doxorubicin, and dexamethasone (VAD) followed by double autologous stem cell transplantation. Patients who achieved stable disease or better were randomized one of three groups: maintenance with pamidronate alone ($n=196$), maintenance with pamidronate and thalidomide ($n=201$), or to no maintenance treatment ($n=200$). The authors did not report whether blinding was used or whether a placebo was given to patients in the control group. The study required two hundred patients in each arm to detect a 15% difference in the three-year risk of skeletal events for the no maintenance arm compared to the pamidronate arm, and to detect a 12% difference in the three-year risk of events for the pamidronate arm compared to

the pamidronate + thalidomide arm with a power of 95% and $\alpha=0.05$. A skeletal event was defined as a bone lesion that required chemotherapy, radiation, or surgery. There were no statistically significant differences in survival, response, or incidence of skeletal events between patients who received pamidronate maintenance compared to patients who received no further treatment (Table 5). However, the pamidronate alone arm had four patients less than the required sample size of 200 patients

A more detailed description is provided for the study reported by Berenson et al.; the initial (20) and longer term results (19) of this double-blind trial comparing pamidronate, 90 mg given intravenously every four weeks, with placebo have been reported. This study enrolled 392 patients, of whom 377 were eligible for analysis. This study differed from the previous studies: only patients with osteolytic lesions and stage III myeloma were eligible, and patients were enrolled at various times points in their disease course. As a result, treatment allocation was stratified according to whether patients were receiving first- or second/subsequent-line chemotherapy. No attempt was made to control the type of chemotherapy received. An initial analysis was done after a median follow-up of nine months (20), and the final results were reported after a median follow-up of 29 months (19). Outcomes of interest included overall survival; a number of skeletal parameters such as progression of bone disease, time to progression, pathologic fractures (total and vertebral), need for surgery or radiation therapy, and spinal cord compression; and the incidence of hypercalcemia. Bone pain, scores for analgesic use, and performance status were measured. Quality of life (measured using the Spitzer index) was also evaluated. No difference in overall survival between groups was detected. The actuarial risks of a skeletal event (reported for both single and aggregate outcome measures) were calculated using the life table method of Kaplan and Meier (28) and compared using the log-rank test (29,30). Using this method of analysis, this study detected a statistically significant difference in some of the skeletal parameters analyzed: after 21 cycles of therapy, more patients randomized to placebo had experienced any skeletal event (58% vs. 50%; $p=0.016$) or a vertebral fracture (36% vs. 23%; $p=0.007$). No differences in the development of any fracture or the incidence of hypercalcemia between groups were detected. More patients randomized to placebo reported pain (71 vs. 61 percent; $p<0.05$). While quality of life was assessed at an interim time point (prior to receiving a ninth cycle of therapy), data were not provided. In the first publication of trial results (20), the authors reported that in comparison with their baseline status, quality of life remained unchanged in patients randomized to pamidronate and deteriorated in patients randomized to placebo. It was not indicated whether the differences between randomized groups differed with statistical significance.

Ibandronate

Ibandronate was evaluated in one RCT. The systematic review included this trial using data that were published in abstract form (25) and provided by the manufacturer. Since the publication of the systematic review, Menssen et al. (24) has reported in article form the results of this double-blind placebo-controlled trial evaluating ibandronate in newly diagnosed and previously treated patients with Durie-Salmon stage II or III myeloma. The chemotherapy regimens used were not defined. Patients were randomized to receive ibandronate 2 mg, given intravenously every four weeks, or placebo. The primary outcome was the number of three-month periods with skeletal events, and secondary outcomes included overall survival, reporting of pain, the development of new lytic lesions, vertebral and non-vertebral fractures, and the development of hypercalcemia. The study included 198 evaluable patients; no statistically significant differences for any outcome measure between groups were detected.

Randomized trials comparing two bisphosphonates

Zoledronate versus pamidronate

One RCT that includes patients with myeloma has been reported in which two bisphosphonates have been compared. Rosen et al. (22) reported the results of a three-arm randomized double-blind comparison of zoledronate 8 mg, zoledronate 4 mg, and pamidronate 90 mg each given every three to four weeks for 13 months in patients with breast cancer or myeloma. Rosen et al. (23) updated these results in 2003. Zoledronate was initially infused over five minutes, but over the course of the study, the protocol was amended to lengthen the duration of infusion to 15 minutes; pamidronate was infused over two hours. Because of concerns of nephrotoxicity, a second amendment subsequently called for patients randomized to receive zoledronate 8 mg to have this dose reduced to 4 mg. Analysis was by intention to treat according to the initial randomization. Eligibility requirements for patients with myeloma included the presence of bone disease and no treatment with a bisphosphonate in the previous twelve months. Patients could be newly diagnosed or previously treated, and the nature of the chemotherapy was not defined. The primary outcome of interest was the incidence of skeletal-related events that were defined to include new pathologic fractures, spinal cord compression, need for radiation therapy or orthopedic surgery, and hypercalcemia. These outcomes were reported both as the number of events occurring and as a time-to-first event. Secondary outcomes of interest included overall and progression-free survival, reporting of pain, and treatment-related toxicities. The trial included 1,648 patients of whom 513 patients had myeloma. No differences in any of the outcomes of interest between groups were detected in the initial report (22). Outcomes for the subgroup of patients with myeloma were reported for both the number of skeletal events and the time-to-first skeletal event; no differences between randomized groups were detected (22). The updated publication (23) reported that patients in the zoledronate group had a reduced risk of multiple skeletal-related events compared to patients in the pamidronate group (risk ratio, zoledronate vs. pamidronate, 0.841; 95% CI 0.719 to 0.983; $p=0.030$). However, for patients with myeloma, the risk of multiple skeletal-related was comparable for both the pamidronate and zoledronate arms (risk ratio, zoledronate vs. pamidronate, 0.932; $p=0.593$) (23).

OSTEONECROSIS OF THE JAW

Literature Search Results

Two-hundred and fifty-two citations were retrieved from MEDLINE and the Cochrane Library databases. Two consensus statement documents (6,31) were identified. In addition, nine case series providing information on incidence or risk factors for development of ONJ were included (32-40). Four case series were reported in abstract form only (32,34,37,39).

Studies

The clinical presentation of ONJ may vary, however, the typical presentation is that of a non-healing ulcer or exposed bone within the oral cavity which may be asymptomatic or in some cases associated with pain or swelling and can lead to significant morbidity including deformity and need for surgical repair (41).

The evidence for an excess risk of ONJ in patients receiving bisphosphonates, while circumstantial, is compelling. ONJ is not restricted to patients receiving bisphosphonates, but has rarely been reported in patients with myeloma prior to 2003, when the first case report linking this complication to bisphosphonate therapy was published. An analysis of a claims database for a large national insurer revealed 224 cases of jaw surgery among 255,757 cancer patients over a three-year period from 2001-2004 (40). The odds ratio of jaw surgery for bisphosphonate users was 4.24 ($p<0.05$), suggesting a marked increase in oral complications in patients treated with these agents. This evidence is supported by a small retrospective series of patients with myeloma that reported ONJ developed in 28/254 (11%) of patients who had

received either pamidronate or zoledronate, while no cases were observed in the 49 patients who did not receive either agent (36). Finally, a dose effect is observed in many of the published series of ONJ with increasing incidence with increasing cumulative dose or duration of therapy (33,35,38,39).

Seven publications estimate the incidence of ONJ in patients with myeloma and other cancers treated with bisphosphonates. Some of those reports were from retrospective reviews of single center experiences while others were from surveys of practitioners. The incidence of ONJ in published series ranges from 1.8% to 12.5% (33-39). A number of factors have been reported to be predictive of development of ONJ in patients with myeloma treated with bisphosphonates (Table 6). Duration of bisphosphonate use or cumulative dose (32,33,35,38,39) and history of dental problems or surgery (32-35,37) were each associated with increased incidence of ONJ in 5/8 published series. One historical cohort comparison compared one year of monthly bisphosphonate followed by a reduction in frequency to every three months to monthly infusions indefinitely as tolerated (32). ONJ was observed in 2% of patients receiving reduced intensity bisphosphonates compared to 12% in those receiving standard monthly dosing. This study must be interpreted with caution as it was not randomized, follow up was shorter in the reduced intensity cohort, dental prevention can be expected to have improved in the more recent cohort, and methodological details are limited as it is presented only in abstract form.

Four series reported higher rates of ONJ in patients treated with zoledronate compared with those receiving pamidronate (32,33,36,38). Factors reported to be associated with ONJ in only one series include older age (35), steroid use (34), anemia (34), and female sex (39).

Table 6. Studies of osteonecrosis of the jaw in patients with multiple myeloma treated with a bisphosphonate.

Study (ref)	N (MM pts)	ONJ (# of pts [%])	Methodology	Predictors
Zappasodi, 2006 (32) Abstract	51 55	6 (12%) 1 (2%)	Retrospective comparison of monthly bisphosphonate infusions vs. a reduced schedule	▪ Intensity of bisphosphonate therapy ▪ Zoledronate use
Durie, 2005 (33)	904	116 (13%)	Web survey of practitioners	▪ History of dental problems ▪ Duration of bisphosphonate use ▪ Zoledronate use
Pozzi, 2005 (34) Abstract	888	16 (2%)	Retrospective survey of centres	▪ Steroid use ▪ Periodontal problems ▪ Anemia
Badros, 2006 (35)	340	11 (3%)	Retrospective review of single centre experience	▪ Dental extraction ▪ Longer follow-up ▪ Older age
Zervas, 2006 (36)	303	28 (9%)	Retrospective review of single centre experience	▪ Zoledronate use ▪ Thalidomide use
Tosi, 2005 (37) Abstract	225	6 (3%)	Retrospective analysis of patients enrolled on prospective trial	▪ Dental extraction/surgery
Dimopoulos, 2006 (38)	202	15 (7%)	Prospective series	▪ Zoledronate use ▪ Duration of bisphosphonate use
Cafro, 2005 (39) Abstract	104	13 (13%)	Retrospective review of two centres	▪ Cumulative dose of bisphosphonate ▪ Female sex

Notes: MM=multiple myeloma, N=number, ONJ=osteonecrosis of the jaw, pts=patients, ref=reference,

Practice Guidelines

The published case series do not specifically address prevention or management of ONJ, however, the two published consensus statements provide recommendations.

Mayo Clinic consensus statement

The Mayo Clinic published consensus recommendations regarding the use of bisphosphonates in multiple myeloma in 2006 (6). This document does not include a systematic review of the literature and does not provide a description of the methodology used, however, it does provide a grading of the evidence and the level of recommendations. The recommendations relating to prevention and/or treatment of ONJ are:

Duration of bisphosphonate therapy:

- Patients should receive monthly infusions of bisphosphonates for 2 years.
- After 2 years, if the patient has achieved remission and is in stable plateau phase off treatment, the bisphosphonates can be discontinued.
- After 2 years, if patients still require active treatment, the frequency of bisphosphonate infusions can be decreased to every 3 months.

Choice of bisphosphonate:

- In patients with newly diagnosed myeloma, we favour the use of pamidronate over zoledronic acid.

Dental evaluation and follow up:

- Have comprehensive dental evaluation before receiving any bisphosphonate treatment
- Undergo invasive dental procedures before starting bisphosphonate treatment.
- See a dentist at least annually and maximize preventive care, report oral/dental symptoms promptly
- Manage new dental problems conservatively and avoid dental extractions unless absolutely necessary
- See an oral and maxillofacial surgeon if surgery is required
- Practice good dental hygiene
- Withhold bisphosphonate treatment for at least 1 month before the procedure and do not resume until the patient has fully recovered and healing of the surgery is complete

American Academy of Oral Medicine

The American Academy of Oral Medicine published a position paper in 2005 on the management of patients with bisphosphonate-associated osteonecrosis (31). The paper makes the following recommendations.

- A dentist should see all patients before intravenous bisphosphonate therapy begins
- A comprehensive extra-oral and intra-oral examination should be performed
- Periodontal health status should be determined and appropriate therapy provided. Pocket elimination is of importance to reduce plaque accumulation, minimize chronic periodontal inflammation and minimize chronic periodontal infections
- Extraction of teeth should be completed as soon as possible
- Restorative dentistry should be performed to eliminate caries and defective restorations
- Prophylaxis should be given and oral hygiene instructions given. The patient should be given information on ONJ and made aware of early signs of development of this condition.
- For patients with ONJ:

- Routine restorative care may be provided. Local anesthetic can be used as necessary
- Scaling and prophylaxis should be done as atraumatically as possible with gentle soft-tissue management
- Avoid dental extractions if possible unless the teeth have a mobility score of 3 or greater.
- Teeth that are extensively carious should be considered for endodontic therapy
- Discontinuation of bisphosphonate therapy:
 - There is no scientific evidence to support discontinuation of bisphosphonates therapy to promote healing of necrotic tissues in the oral cavity.
 - One must consider the risks and benefits of discontinuation

DOSING AND SCHEDULING

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 (42).

- a) **Clodronate:** Administration of clodronate has been reported to aggravate renal function in some patients. Monitoring of renal function is recommended, particularly when clodronate is given intravenously. The product monograph described in the Compendium of Pharmaceuticals and Specialties (42) indicates that clodronate is contraindicated when serum creatinine values exceed 440 $\mu\text{mol/L}$. For patients with a serum creatinine between 220-440 $\mu\text{mol/L}$, a dose reduction should be considered or the agent should be withheld.
- b) **Pamidronate:** Pamidronate has been reported to be associated with the development of proteinuria and renal dysfunction secondary to glomerulosclerosis (43). This risk appears to be greater when pamidronate, 90 mg per dose, is administered over less than four hours (22.5 mg/hour). Serum creatinine and urinary protein levels should be regularly monitored in patients receiving pamidronate, and the drug should be withheld if renal dysfunction or proteinuria is observed. Although pamidronate is excreted unchanged by the kidney, the drug has been safely used in patients with pre-existing renal dysfunction, including patients undergoing dialysis. Experience with patients with creatinine levels greater than 440 $\mu\text{mol/L}$ is limited. Pamidronate should be used with caution in such situations, and renal function should be monitored (43). No dose modification is required for renal dysfunction.
- c) **Zoledronate:** Nephrotoxicity has been reported in patients receiving zoledronate, particularly when using doses greater than 4 mg or when the drug is infused in less than 15 minutes (22). Serum creatinine and urinary protein levels should be regularly monitored. For patients with serum creatinine levels greater than 440 $\mu\text{mol/L}$, the use of zoledronate is not recommended. No dose modification is required for patients with renal dysfunction.

DISCUSSION

Interpretation of the RCTs evaluating bisphosphonate use in patients with myeloma is complex. Variables differing among studies include the patient populations studied (e.g., presence or absence of bone disease, stage of disease, and degree of previous chemotherapy treatment), the specifics of the treatment manoeuvre (e.g., type of bisphosphonate given and route of drug administration), and the considerable heterogeneity in the nature of the outcome measures assessed. As assessment of most outcome measures could be associated with

observer bias, greater weight should be given to the data provided by double-blinded RCTs that include the use of a placebo agent in the control population.

The reported RCTs have included a variety of outcome measures that include measures of mortality, bone disease (e.g., all fractures, vertebral or non-vertebral fractures, new or progressive osteolytic lesions, and hypercalcemia), need for intervention (radiation therapy and orthopedic or neurosurgical procedures), and metabolic parameters of bone disease. These outcomes have been reported as individual and aggregate measures and as time-to-event measures or as a proportion of patients suffering an event within a defined time period.

Based on a review of 13 RCTs, consistent evidence is provided to indicate that the use of a bisphosphonate reduces the number and severity of bone complications in patients with myeloma. This evidence is strongest in supporting a role for using oral clodronate, intravenous pamidronate, or intravenous zoledronate and in demonstrating that the use of these agents reduces the risk of vertebral body fractures. Although less consistent, some trials have detected a reduction in other skeletal events. The results of a published data meta-analysis confirm that bisphosphonates reduce vertebral fractures and also describe a reduction in pain in patients treated with these agents. The meta-analysis failed to detect significant differences in other fractures, incidence of hypercalcemia, or overall survival. In comparison with placebo or no treatment, RCTs have not detected benefits associated with the use of etidronate, oral pamidronate, or ibandronate.

Randomized trials have not reported significantly increased treatment-related toxicities in patients treated within the bisphosphonate arms of the trials. Despite this, increasing evidence is emerging from other sources implicating the intravenous bisphosphonates, pamidronate and zoledronate, in the development of osteonecrosis of the jaw as well as development of nephrotoxicity. These toxicities, while rare can be associated with significant morbidity.

Only one RCT has included a comparison of different bisphosphonate agents; no clinically important differences were detected in a comparison of intravenous pamidronate with zoledronate. The magnitude of benefit seen within individual trials does not provide clear evidence indicating the superiority of one bisphosphonate agent over another. Case series of patients with ONJ suggest an increased incidence of this complication in patients treated with zoledronate.

The recommendations in this guideline are, in large part, consistent with those of the American Society of Clinical Oncology (ASCO). Minor differences between the two sets of recommendations do exist, however. The first difference relates to the choice of bisphosphonate. The ASCO guideline recommends the use of intravenous pamidronate or zoledronate. They acknowledge that evidence of benefit exists for the use of clodronate but identifies pamidronate and zoledronate as superior agents on the basis that: clodronate had not yet been approved for use in the US; there were methodological issues in the studies evaluating clodronate that might result in an over-estimation of benefits (due to use of events per year rather than a time-to-event analysis); there was incomplete follow-up in one of the studies evaluating clodronate; and that, in the clodronate studies, all skeletal-related outcome measures had not been aggregated into a single endpoint. While the ASCO guideline addresses important potential methodological limitations in the studies assessing oral clodronate, this agent is approved for use in this indication in our jurisdiction. The DSG concluded that the methodological concerns over the nature of the endpoints were not a significant concern given the consistent evidence of benefit for clodronate in the systematic review. The more important parameters influencing patient choice may be factors such as the route of administration, tolerance, and overall convenience of the agent.

Another minor difference exists over the recommendations for patients without lytic bone lesions. Most published trials included only patients with myeloma and established bone disease. The indication for using a bisphosphonate in patients with myeloma who do not have bone disease is less well established; only one trial (10,11) included these patients. In that trial

testing oral clodronate, a comparable reduction in vertebral fracture rates was seen in the groups with and without pre-existing bone disease at study entry. However, as the total number of patients evaluated in this situation is small, that evidence does not permit recommendations as strong as those provided for patients with bone disease. On the strength of this evidence, we recommend that patients should be offered therapy with a bisphosphonate. The ASCO guidelines, on the basis of consensus, recommend a bisphosphonate be used for patients with osteopenia but no lytic lesions, but do not make a specific recommendation for patients without any evidence of bone disease. The ASCO guidelines also specifically state that a bisphosphonate not be recommended for patients with solitary plasmacytoma, monoclonal gammopathy of uncertain significance, or smouldering myeloma on the basis of consensus rather than direct evidence. We did not specifically address this population in our guideline document, but agree with this interpretation of the data. We do not recommend a bisphosphonate in this population if no other indication exists.

The consensus statements of the Mayo clinic and the Academy of Oral Medicine were reviewed by the DSG and considered to represent expert opinion rather than being rigorously developed practice guidelines. Though neither included a systematic review component, both cited many of the references that we identified. In the absence of high quality data from randomized trials or properly conducted guidelines, the DSG developed recommendations by expert consensus based on lower quality evidence. The DSG endorsed the recommendations of the Mayo Clinic consensus statement and the position paper of the Academy of Oral Medicine as outlined below. The DSG discussed the recommended duration of bisphosphonate therapy extensively. This is a question with great clinical relevance, but one for which little direct high-quality evidence exists. In the previous iteration of this guideline, the DSG had endorsed chronic long-term bisphosphonate therapy, largely generalizing upon data from RCTs with up to 2 years of therapy. The increasing reports of osteonecrosis of the jaw, the results of the study of Attal et al (15), which did not demonstrate a benefit for bisphosphonates following initial therapy with autologous stem cell transplantation, and the consensus statements from the Mayo Clinic and Academy of Oral Medicine influenced the DSG's decision to recommend consideration of discontinuation or less frequent administration of bisphosphonates after 2 years of therapy. These recommendations are based largely on expert consensus and should be revisited when further evidence becomes available.

CONCLUSIONS

The members of the 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 NNT of 10 to prevent one patient with a vertebral fracture and a NNT 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, given the evidence suggesting a higher rate of ONJ with intravenous zoledronate and the perception that monthly intravenous infusions were better tolerated than daily oral therapy with clodronate. Unlike the ASCO expert panel, the DSG did not feel that the evidence clearly favoured intravenous pamidronate or zoledronate over clodronate.

- c) **Duration of therapy:** Both the clodronate and pamidronate trials suggest that at least 24 months is beneficial. Given the emerging evidence that prolonged bisphosphonate therapy is a risk factor for development of ONJ, the DSG endorsed the Mayo Clinic recommendations that after 2 years bisphosphonates treatment should be stopped in patients who achieve a remission and are stable off of therapy and that consideration can be given to decreasing frequency to every three months in patients still requiring active treatment. Bisphosphonate therapy may also be of benefit in palliation of pain associated with progressive bone disease and should be continued on a monthly basis when used for this indication.
- d) **Prevention and management of ONJ:** The DSG recognized that no high quality evidence exists to guide clinicians in the prevention and management of this complication. The DSG strongly endorsed the recommendations of the Mayo clinic and American academy of Oral Medicine to increase patient and clinician awareness of this complication, to promote oral hygiene and regular dental assessment as well as minimizing invasive dental procedures where possible. The DSG did not consider the recommendation of the Mayo Clinic Consensus Statement to withhold bisphosphonates for one month prior to dental procedures to be supported by data or the pharmacokinetics of these agents. The American Academy of Oral Medicine does not recommend discontinuation of bisphosphonates for a set period prior to dental work and only recommend that risks and benefits of discontinuation be considered. The DSG endorse this latter approach.

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 lesions, osteopenia, or osteoporosis, health care providers should inform patients of the potential benefits and risks of therapy and offer treatment with a bisphosphonate
- Evidence exists to support the use of clodronate (800 mg orally twice daily), pamidronate (90mg 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 a alternative agent
- It is recommended that patients be treated for a minimum of two years.
- After two years of bisphosphonate treatment:
 - Patients who have achieved remission and are in stable plateau phase off treatment, should consider discontinuing the use of bisphosphonates.
 - Patients who still require active treatment for their myeloma, should continue on bisphosphonates, but may consider having the frequency decreased to every three months if on pamidronate or zoledronate.
- Patients whose myeloma becomes active following an initial response should resume monthly bisphosphonate therapy while on active treatment.

- Patients receiving bisphosphonates should have comprehensive dental evaluation before or soon after starting bisphosphonate treatment, undergo invasive dental procedures, if needed, before starting bisphosphonate treatment.
- Patients should be followed by dentistry and should be made aware of the importance of oral hygiene and of the early signs of ONJ.

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 $\mu\text{mol/L}$. 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.

ONGOING TRIALS

The National Cancer Institute's clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and the United States National Institutes of Health Clinical Trials database (<http://clinicaltrials.gov/>) were searched for reports of new or ongoing trials that involved use of bisphosphonates to treat skeletal-related complications in patients with multiple myeloma. The Hematology DSG identified the following randomized trials:

Protocol ID	Title and details of trial
NCT00330759	Double-Blind Study of Denosumab Compared With Zoledronic Acid in the Treatment of Bone Metastases in Subjects with Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma. Outcomes: not reported. Projected accrual: not reported. Accessed: January 15, 2007. Available at: http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=489204&version=HealthProfessional&protocolsearchid=2987055 .
NCT00424983	Pharmacokinetic, Pharmacodynamic, and Safety Study of Zoledronic Acid Administered Monthly vs. Every 3 Months in Multiple Myeloma Patients and Breast Cancer Patients Who Have Been Treated with Zoledronic Acid for the Prior Year. Outcomes: pharmacokinetics, pharmacodynamics, skeletal-related events (number and time-to-event), and pain. Projected accrual: 72 patients. Accessed: January 15, 2007. Available at: http://clinicaltrials.gov/ct/show/NCT00424983?order=1 .
NCT00171925	Therapy With Zoledronic Acid in Patients With Multiple Myeloma Stage I. Outcomes: progression-free survival, overall survival, skeletal-related complications, quality of life. Projected accrual: 220 patients. Accessed: January 15, 2007. Available at: http://clinicaltrials.gov/ct/show/NCT00171925?order=1 .

NCT00216151 A Randomized Phase II Study of Bisphosphonates: Zoledronic Acid (Zometa) in the Management of Asymptomatic/Early Stage Multiple Myeloma. Outcomes: change in bone mineral density of the spine, percent change in bone mineral density of the total hip and femur. Projected accrual: 84 patients. Accessed: January 15, 2007. Available at: <http://clinicaltrials.gov/ct/show/NCT00216151?order=1>.

CONFLICT OF INTEREST

The members of the Hematology DSG were asked to disclose potential conflicts of interest relating to the topic of this systematic review. No potential conflicts were declared.

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For a complete list of the Hematology Disease Site Group members please visit the PEBC section of the CCO Web site at <http://www.cancercare.on.ca/>

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Evidence-based Series 6-4: Section 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

The Role of Bisphosphonates in the Management of Skeletal Complications for Patients with Multiple Myeloma: Guideline Development and External Review - Methods and Results

*K. Imrie, A. Stevens, J. Makarski, R. Esmail, J. Meharchand, R. Meyer,
and the members of the Hematology Disease Site Group*

Original Report Date: March 30, 2004

Current Report Date: March 12, 2007

The 2007 guideline recommendations require an

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*

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-Based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-Based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline.* This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review: Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Hematology DSG of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on the role of bisphosphonates in the management of skeletal complications for patients with multiple myeloma, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

External Review by Ontario Clinicians

Draft Recommendations

Based on the evidence described above, the Hematology DSG drafted the following recommendations:

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review August 26, 2003)
<i>Target Population</i> These recommendations apply to adult patients with active plasma cell myeloma (symptomatic stage 1 or greater).
<i>Recommendation</i> • It is recommended that all patients with myeloma who have bone disease receive a bisphosphonate. • For patients with myeloma who do not have bone disease, 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.⁷
<i>Qualifying Statements</i> • 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 proteinuria or an increasing serum creatinine should have the bisphosphonate withheld pending additional evaluation. • Clodronate is contraindicated in patients with a serum creatinine value greater than 440 µmol/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.

Methods

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 above 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 DSG reviewed the results of the survey.

Results

Forty-six responses were received out of the 115 surveys sent (40% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 30 indicated that the report was relevant to their clinical practice and completed the survey. Key results of the practitioner feedback survey are summarized in Table 6.

Table 6. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a clinical practice guideline, as stated in the "Choice of Topic" section of the report, is clear.	30 (100)	0	0
There is a need for a clinical practice guideline on this topic.	28 (93)	2 (7)	0
The literature search is relevant and complete.	28 (93)	2 (7)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	29 (97)	0	1 (3)
The draft recommendations in this report are clear.	28 (93)	0	2 (7)
I agree with the draft recommendations as stated.	27 (90)	2 (7)	1 (3)
This report should be approved as a practice guideline.	27 (90)	2 (7)	1 (3)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice? ^a	Very likely or likely	Unsure	Not at all likely or unlikely
	23 (79)	3 (10)	3 (10)

^aOne practitioner did not provide a response to this question.

Summary of Written Comments

Of the 30 respondents who indicated that this guideline was relevant to their practice, nine (30%) provided written comments. The main points were:

1. Two respondents stated that bone disease (e.g., lytic lesions, osteopenia, osteoporosis) should be more clearly defined.

2. With respect to managing patients who do not demonstrate features of bone disease, two respondents stated that the wording of the guideline (“inform patients of the potential benefits and risks of therapy and offer treatment with a bisphosphonate”) provides insufficient guidance.
3. Two respondents stated that, in comparison with pamidronate or zoledronate, there is insufficient evidence to support use of clodronate. One of these respondents indicated concern of potential funding implications for treatment if this guideline were to lead to preferential funding for clodronate in place of pamidronate.
4. One respondent indicated that it is unnecessary to withhold bisphosphonate treatment as a result of progressive proteinuria.

Modifications/Action

1. Members of the DSG concurred that “bone disease” could be better defined. Recommendations have been modified to explicitly define bone disease as “lytic bone lesions, osteopenia, or osteoporosis”
2. With respect to managing patients who do not demonstrate features of bone disease, and in comparison with the recommendation to use a bisphosphonate in patients who do demonstrate features of bone disease, members of the DSG appreciate that the current wording of the guideline provides a less explicit directive. Based on available evidence, the DSG confirmed that current wording of this recommendation remains appropriate. While sufficient evidence exists to make treatment with a bisphosphonate a reasonable option for these patients, this evidence is less robust than that described for patients with bone disease and therefore should be framed in a manner that places a greater weight on individual patient preferences. No changes were made to the recommendation.
3. With respect to the choice of bisphosphonate, members of the DSG confirmed the current recommendation that clodronate, pamidronate, and zoledronate are appropriate options for treatment. The DSG based this conclusion on the positive results of individual trials and the Cochrane review, and the lack of direct comparisons of clodronate with other agents. The DSG concurred that pamidronate or zoledronate may be preferred over clodronate based on a perception that monthly infusions are better tolerated. No changes were made to the recommendation.
4. With respect to the continued use of a bisphosphonate in the presence of progressive proteinuria, the DSG disagreed with the comment of the respondent who indicated that modification of bisphosphonate therapy was unnecessary. Based on reports of progressive glomerular disease, the DSG confirmed the current recommendation to withhold bisphosphonate therapy pending further evaluation. However, the DSG did modify the recommendation to use the term “albuminuria” rather than “proteinuria” in order to exclude from this recommendation progressive urinary light-chain excretion that might result from progressive myeloma. The DSG also added to the recommendation a statement that the reintroduction of bisphosphonate therapy at a slower infusion rate (for intravenous formulations) could be considered for patients demonstrating resolution of the progressive albuminuria or increasing serum creatinine.

Practice Guidelines Coordinating Committee Approval Process

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.

The one member commented that “the real clinical question” is whether bisphosphonates should be used in patients without bone disease and requested that the report be clarified in terms of which evidence was for patients with and without bone disease. This comment was accompanied by suggested changes to the *Target Population*, *Recommendations*, and *Key Evidence* sections, an addition to the *Qualifying Statements* section, and the description of patient populations of trials regarding this issue throughout the report. In addition, the PGCC member requested that the last sentence of the Key Evidence bullet regarding the Cochrane systematic review be modified or deleted in light of current knowledge on zoledronate and to specify the McCloskey clodronate trial comparison group in the last paragraph of the Interpretive Summary. Other comments for consideration from the PGCC were to provide a summary of answers to the guideline questions before stating the recommendations in order to clearly answer the guideline questions for the readership and to include the subgroup survival analysis in the Berenson pamidronate trial because of the impression that these data have influenced thinking.

Modifications/Actions

No changes were made to the guideline in response to the comments made by the PGCC. The Hematology DSG agreed that the benefits of bisphosphonate therapy in patients without bone disease is a complex issue. The DSG addressed this issue as a specific item during their discussions, as noted in the Interpretive Summary and DSG Consensus sections of the document, and with a specific bullet in the Recommendations section. The DSG recognizes that there is a lesser weight of evidence to support the recommendation to treat patients without bone disease but concluded that available evidence is generalizable to these patients. The DSG had already phrased the recommendation to treat patients without bone disease in a more moderate manner by using the terms “inform” and “offer”.

The sentence in the *Key Evidence* section regarding the systematic review accurately reflects the conclusions in the systematic review: only placebo-controlled trials were reviewed, thus excluding the trial comparing zoledronate with pamidronate. Regarding the clodronate trial, details of this are provided in the *Results* section and were therefore not repeated in the *Interpretive Summary*. Regarding the comment to address potential differences in overall survival based on subgroup analyses of the Berenson trial, the DSG chose not to report the details of this analysis given the nature of that subgroup analysis, and the failure to detect a difference, or trend towards a difference, in overall survival in the meta-analysis.

Policy Review

An earlier version of this guideline was submitted to the PAC in October 1997; the submitted guideline was in draft form and not yet circulated for practitioner feedback. In the fall of 1997, the Ontario Ministry of Health approved new drug funding for pamidronate. Conclusions following practitioner feedback were presented to PAC in November 1999.

This guideline was submitted to the PAC for the March 30, 2004 PAC meeting for the following reasons: to inform the PAC of issues regarding bisphosphonate treatment for myeloma, to prompt a discussion regarding a policy for use of zoledronate in patients with myeloma, and to update their endorsement of the policy regarding pamidronate. At time of submission, the guideline was approved by the PGCC.

In February 2007 the PEBC submitted this evidence-based series to the Committee to Evaluate Drugs (CED) CCO subcommittee as part of a review addressing the duration of use of bisphosphonates and the occurrence of osteonecrosis of the jaw in patients with myeloma.

2006 Update

In December 2006, the Hematology DSG agreed that the original March 2004 practice guideline was in need of an update. The practice guideline was reformatted into an evidence-based series. In addition, the Hematology DSG added additional questions to address the association of bisphosphonate therapy with osteonecrosis of the jaw, in response to emerging evidence linking this complication to bisphosphonate treatment. The following questions were added to the evidence-based series:

What is the association of bisphosphonates with osteonecrosis of the jaw? How can this complication be prevented and managed?

The original literature search was updated to identify any new evidence regarding the role of bisphosphonates in managing skeletal complications in patients with myeloma. A second literature search was developed to identify studies that reported on the incidence or risk factors for development of osteonecrosis of the jaw (ONJ) in patients with multiple myeloma who were treated with a bisphosphonate. The following eligibility criteria were developed for the ONJ literature search:

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 that reported on the incidence or risk factors for development of ONJ:

1. Systematic reviews, meta-analyses, or practice guidelines evaluating the use of bisphosphonates 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.
3. Case series of patients with multiple myeloma who receive treatment with a bisphosphonate.

Exclusion Criteria

1. Studies that included patients with various types of malignancies in which the results for patients with myeloma were not reported separately.
2. Reports published in a language other than English.

The update of the original literature search and the development of the new literature search identified several new studies for inclusion in the systematic review of this evidence-based series. That evidence was used to inform and update the recommendations found in the practice guideline section of this evidence-based series. No changes were made to the existing recommendations. However, the following recommendations were added in order to address the issue of ONJ:

- It is recommended that patients be treated for a minimum of 2 years.
- After 2 years of bisphosphonate treatment:

- Patients who have achieved remission and are in stable plateau phase off treatment, should consider discontinuing the use of bisphosphonates.
- Patients who still require active treatment for their myeloma, should continue on bisphosphonates, but may consider having the frequency decreased to every 3 months if on pamidronate or zoledronate.
- Patients whose myeloma becomes active following an initial response should resume monthly bisphosphonate therapy while on active treatment.
- Patients receiving bisphosphonates should have comprehensive dental evaluation before or soon after starting bisphosphonate treatment and undergo invasive dental procedures, if needed, before starting bisphosphonate treatment.
- Patients should be followed by dentistry, should be made aware of the importance of oral hygiene, and of the early signs of ONJ.

Conclusion

This report reflects the integration of feedback obtained through the external review process with final approval given by the Hematology DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. *J Clin Oncol.* 1998;16(3):1226-31.

The Role of Bisphosphonates in the Management of Skeletal Complications for Patients with Multiple Myeloma

Guideline Review Summary

Review Date: October 23, 2012

The 2007 guideline recommendations require an

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 the Program in Evidence-based Care, Cancer Care Ontario, in 2004 and was updated in March 2007. In September 2011, the PEBC guideline update strategy was applied and the new document to be updated released in October 2012. The recommendations and the systematic review in this version are the same as March 2004 version.

Update Strategy

Using the Document Assessment and Review Tool, 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

For patients with active multiple myeloma is there evidence that the use of bisphosphonates:

1. Improves survival?
2. Improves quality of life?
3. Reduces bone pain?
4. Reduces or delays the development of skeletal complications?

For patients with multiple myeloma who receive treatment with a bisphosphonate:

5. What is the association of bisphosphonates with osteonecrosis of the jaw (ONJ)?
6. How can this complication be prevented and managed?

Literature Search and New Evidence

The new search (Jan 2007 to May 2011) yielded 15 relevant new publications representing one case series, six randomized controlled trials (RCTs), one meta-analysis (abstract), and seven guidelines. Brief results of these publications are shown in the Document Assessment and Review Tool below.

Impact on Guidelines and Its Recommendations

The new data does not contradict existing recommendations. However, new recommendation in patients without lytic bone disease will need to be considered. The Hematology DSG decided that the 2007 recommendations on the role of bisphosphonates in the management of skeletal complications for patients with multiple myeloma require an [UPDATE](#).

Document Summary and Review Tool

Number and title of document under review	The Role of Bisphosphonates in the Management of Skeletal Complications for Patients with Multiple Myeloma
Current Report Date	March 12, 2007
Clinical Expert	Dr. Matthew Cheung
Research Coordinator	Chika Agbassi
Date Assessed	Sept 2011
Approval Date and Review Outcome (once completed)	23 October 2012 [TO BE UPDATED]
<u>Original Question(s):</u> For patients with active multiple myeloma, is there evidence that the use of bisphosphonates: 1. Improves survival? 2. Improves quality of life? 3. Reduces bone pain? 4. Reduces or delays the development of skeletal complications? For patients with multiple myeloma who receive treatment with a bisphosphonate: 5. What is the association of bisphosphonates with osteonecrosis of the jaw (ONJ)? 6. How can this complication be prevented and managed? <u>Target Population:</u> These recommendations apply to adult patients with active plasma cell myeloma (symptomatic stage 1 or greater). <u>Study Selection Criteria:</u> 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.

Search Details:

- Jan 2007 to May 2012 (Medline and Embase, ASCO Annual Meeting, ASH Meeting abstract, and Clinicaltrials.gov)

Brief Summary/Discussion of New Evidence:

Of 234 total hits from Medline + Embase and 5 total hits from ASCO + ASH conference abstract searches, 15 references representing One case series, 6 RCT, one meta-analyses (abstract) and 7 guideline were found.

Interventions	Name of RCT (med F/U)	Population (n)	Outcomes	Brief results	References
Bisphosphonate vs. Placebo/Observation/no treatment bisphosphonate					
Bisphosphonate vs. placebo/no treatment	Meta-analysis of 17 RCTs	(n= 3010)	OS, PFS, SRE TTE, pain. Hypercalcemia,	BIS was significantly beneficial in the prevention of PVF: RR=0.74 (95%CI 0.62-0.89) p=0.001 SRE: RR= 0.81(95%CI 0.72-0.92) p=0.001 and amelioration of pain; RR=0.75 (95%CI 0.60-0.95) p=0.01 There were no significant differences in OS, PFS, hypercalcemia and non-vertebral fractures.	Mhaskar R. et al 2009 [ABSTRACT]
Pamidronate 30mg to 90mg q4W x1yr vs. Observation	(5yrs)	Asymptomatic (n=177)	TTE, SREs OS	PAM significantly reduced the incidence of SRE compared to observation. There was no significant difference between the treatment arms in OS and TTP	D'Arena G. et al 2011
Zoledronic Acid (4mg q3-4W) vs. Observation	(64.7p/m)	Asymptomatic (163)	SRE	SRE was significantly lower in the ZOL group (55.5%) than the observation group (78.3%) p=0.041	Musto P. et al 2008
Zoledronic Acid (4mg q3-4W) vs. Observation	(49.6m)	Previously untreated Age ≥ 18yrs ECOG PS <3 (n=94)	EFS, OS SRE-Prevention	ZOL was significantly better than observation in EFS: 80% versus 52%. and OS 80% versus 46% p<0.01 SRE was more frequent in the observation arm	Aviles A. et al 2007
Zoledronic Acid (4mg q3-4W) vs. Observation	N/A	Stage 1 Age >18yrs (n=140)	PFS TTE safety	There was no significant difference between arms.	Sezer O. et al 2010 [ABSTRACT]
bisphosphonate vs. bisphosphonate					
Zoledronic Acid (4mg q3-4W) vs. Clodronic acid 1600mg qd	MRC myeloma IX (3.7yrs)	Newly diagnosed Age ≥ 18yrs (n=1960)	OS, DFS, ORR	Compared to CLO, ZOL significantly • Reduced mortality by 16% HR = 0.84 (95 %CI 0.74-0.96) p= 0.0118 and median survival was extend by 5.5mos. • Improved PFS by 12% (HR = 0.88 ; 95 %CI 0.80-0.968) p= 0.0179 and median PFS was increased by 2mos • Lowered the incidence of SREs (HR=0.74; 95%CI 0.62-0.87) p=0.0004 ORR was not significantly different between groups but rate of ONJ was higher in the ZOL group (4%) against 1% in the CLO arm	Morgan G. et al 2011 Mor gan G. et al 2010
Pamidronate 30mg vs. 90mg q4W x 3yrs	(12m)	(n=504)	PF	There was no significant difference between the two groups but more patient developed ONJ in the 90mg group.	Gimsing P et al 2010
Case series.					
Non-exposed variant of bisphosphonate associated ONJ	N/A	(n=96)		Clinical features of non-exposed osteonecrosis include; Jaw bone pain, sinus tract, bone enlargement, gingival swelling.	Fedele S. et al 2010

CLO=clodronic acid; d=days; DFS= disease free survival; EFS= event free survival; HR= hazard ratio; m=months; n= number enrolled; N/A= not available; ONJ=osteonecrosis of the jaw. ORR= overall response rate; OS= overall survival; PF= physical unction; p/m= person per month; PVF= pathologic vertebral fracture; q= every; RR= risk ratio; W=weeks; SRE=skeletal related events; TTE= time to event; ZOL=zoledronic acid; vs.=versus.

Instructions. These questions are answered by the Clinical Expert assigned by the DSG/GDG. Beginning at question 1 answer the questions in order, following the instructions in the black boxes as you go.	
1. 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:	1.No If Yes, the document will be immediately removed from the PEBC website, and a note as to its status put in its place. Go to 2.
2. On initial review, a. Does the newly identified evidence support the existing recommendations? b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No to each, and explain if necessary:	2.a - Yes. The new evidence continues to support the recommendation for use of bisphosphonates in patients with lytic bone disease. 2b. - No. A new recommendation in patients without lytic bone disease will need to be considered in light of the MRC trial comparing ZOL and CLO, and demonstrating an OS benefit in the ZOL arm. If both are Yes, the document can be ENDORSED . If either is No, go to 3.
3. 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:	3. No. If Yes, a final decision can be DELAYED up to one year. If No, go to 4.
4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year?	4. No. Given the limitation in number of active documents and recent prioritization by the Hematology DSG, the group may not have adequate resources to update this document within a 1-year timeframe. If Yes, the document needs an UPDATE . It can be listed on the website as IN REVIEW for one year. If a full update is not started within the year, it will be automatically ARCHIVED . If NO, go to 5.
5. If Q2, Q3, and Q4 were all answered NO, this document should be ARCHIVED with no further action.	
Review Outcome	TO BE UPDATED
DSG/GDG Approval Date	October 23, 2012
DSG/GDG Commentary	There is substantial new information that makes the current version outdated. Ideally, the guideline should be updated but it is less certain about whether an updated guideline has an important potential to influence practice either by informing clinicians or through facilitation of funding. Given the opportunity cost and competing priorities there may be areas where greater gains could be realized.

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Literature Search Strategy:

MEDLINE

1. meta-Analysis as topic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. meta analysis.pt.
3. (meta analy\$ or metaanaly\$).tw.
4. (systematic review\$ or pooled analy\$ or statistical pooling or mathematical pooling or statistical summar\$ or mathematical summar\$ or Quantitative syntheses or quantitative overview?).tw.
5. (systematic adj (review\$ or overview?)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (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.
9. (reference list\$ or bibliograph\$ or hand-search\$ or relevant journals or manual search\$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
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. (clinic\$ adj trial\$1).tw.
24. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3 or dummy)).tw.
25. placebos/
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. myeloma/ or multiple myeloma/
37. bisphosphonates.mp. or bisphosphonic acid derivative/
38. (pamidronate or neridronate or olpadronate or alendronate or ibandronate or risedronate or zoledronate).tw.
39. 37 or 38
40. 36 and 39
41. 35 and 40
42. (2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or "2012").ed.
43. 41 and 42
44. limit 43 to (english language and humans)

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 synthes?s 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. (clinic\$ 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.
26. practice guideline.pt.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
30. 28 not 29
31. myeloma/ or multiple myeloma/
32. bisphosphonates.mp. or bisphosphonic acid derivative/
33. (pamidronate or neridronate or olpadronate or alendronate or ibandronate or risedronate or zoledronate).tw.
34. 32 or 33
35. 31 and 34

- 36. 30 and 35
- 37. (2007\$ or 2008\$ or 2009\$ or 2010\$ or 2011\$ or "2012").ew.
- 38. 36 and 37

OUTCOMES DEFINITIONS

1. **ARCHIVED** - 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 the Web site and each page is watermarked with the phrase "ARCHIVED".
2. **ENDORSED** - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG 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. **DELAY** - A Delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.
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.