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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

Members of the Hematology Disease Site Group

This Evidence-based Series (EBS) was reviewed in September 2011 and on October 23 2012 the Hematology Disease Site Group (DSG) made a decision to UPDATE it.
The reviewed EBS report consists of 4 sections and is available on the CCO Web site (http://www.cancercare.on.ca) PEBC Hematology DSG page at https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/hema-ebs/.
Section 1: Clinical Practice Guideline (TO BE UPDATED)
Section 2: Systematic Review
Section 3: Guideline Development and External Review
Section 4: Guideline Review Summary

Release Date: October 30, 2012

For information about this document, the PEBC, and/or all versions of reports, please visit the CCO Web site at http://www.cancercare.on.ca/
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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.

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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 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.

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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