



Evidence-based Series #6-4: Section 1

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*

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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?
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 an 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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Contact Information

For further information about this series, please contact:

Dr. K. Imrie, Co-Chair, Hematology Disease Site Group, Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5; TEL (416) 480-4757; FAX (416) 480-6002;

or

Dr. C.T. Kouroukis, Co-Chair, Hematology Disease Site Group, Juravinski Cancer Centre, 699 Concession Street, Hamilton, Ontario, L8V 5C2; TEL (905) 387-9711 ext. 62484; FAX (905) 575-6340.

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