

IMWG Guidelines for the Use of Bisphosphonates in Myeloma

Intravenous bisphosphonate therapy has been amply demonstrated to reduce bone complications of myeloma. Bisphosphonate (BP) therapy is therefore an important component of supportive care for myeloma patients with bony disease. Adverse events associated with BP are usually mild and consist of fever, renal function impairment, myalgias, and hypocalcemia. A more serious potential side effect of bisphosphonate therapy that was first identified in 2003¹ is osteonecrosis of the jaw (ONJ), a debilitating problem that can be associated with significant morbidity.

The following guidelines for the use of bisphosphonate therapy in myeloma are based upon IMWG and Mayo Clinic guidelines^{2,3} and are intended to provide safe criteria for bisphosphonate use to minimize risk and maximize benefit:

- Bisphosphonate therapy administered monthly is appropriate for patients with overt myeloma-related lytic bone disease on radiographs and/or MRI and/or PET/CT.
- Bisphosphonate (BP) use is not recommended in patients with smoldering myeloma.
- Given the higher rate of ONJ in patients receiving long-term zoledronic acid, pamidronate or clodronate (outside the U.S.) is preferred for longer-term use (> 2 years).
- Pretreatment comprehensive dental evaluation is important in patients who will receive intravenous BP. After BP therapy has been initiated, patients should see a dentist at least annually, and elective procedures such as extractions should be attempted only after careful consideration of the risk of ONJ.
- BP use should not be indefinite or open-ended.
- In patients who have achieved a complete or very good partial response and have no active bone disease, BP therapy is not recommended beyond the first year.
- For patients with less than a very good partial response and/or on-going bone disease, further BP use is recommended; however after two years patients without active bone disease can discontinue BP use.
- In patients who relapse with new bone disease, BP therapy with pamidronate or clodronate should be reinstated. Careful monitoring of dental status and renal function is required with long-term BP use.
- Patients who develop ONJ should discontinue BP use.

The following table from the American Association of Oral and Maxillofacial Surgery Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw (approved September 25, 2006) presents their recommendations for staging and treatment strategies:

BRON† Staging	Treatment Strategies‡
At risk category No apparent exposed/necrotic bone in patients who have been treated with either oral or IV bisphosphonates	<ul style="list-style-type: none"> • No treatment indicated • Patient education
Stage 1 Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection	<ul style="list-style-type: none"> • Antibacterial mouth rinse • Clinical follow-up on a quarterly basis • Patient education and review of indications for continued bisphosphonate therapy
Stage 2 Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	<ul style="list-style-type: none"> • Symptomatic treatment with broad-spectrum oral antibiotics, e.g. penicillin, cephalexin, clindamycin, or 1st generation fluoroquinolone • Oral antibacterial mouth rinse • Pain control • Only superficial debridements to relieve soft tissue irritation
Stage 3 Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra-oral fistula, or osteolysis extending to the inferior border	<ul style="list-style-type: none"> • Antibacterial mouth rinse • Antibiotic therapy and pain control • Surgical debridement/resection for longer term palliation of infection and pain

1 Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic [letter]. *J Oral Maxillofac Surg.* 2003;61:1115-1117.

2 Durie BGM *Mayo Clin Proc.* April 2007;82(4):516-522,[letter]

3 Lacy MQ et al. *Mayo Clin Proc.* August 2006;81(8):1047-1053

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American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws

<http://myeloma.org/pdfs/AAOMSosteonecrosis.pdf>

Use of Bisphosphonates in Multiple Myeloma: IMWG Response to Mayo Clinic Consensus Statement

<http://myeloma.org/pdfs/MayoClinProc.pdf>

Mayo Clinic Consensus Statement for the Use of Bisphosphonates in Multiple Myeloma

<http://myeloma.org/pdfs/MayoConsensusBis.pdf>