

LETTERS TO THE EDITOR

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

To the Editor: The International Myeloma Working Group (IMWG), which comprises 85 investigators specializing in the area of multiple myeloma, has reviewed and considered the recent Mayo Clinic consensus statement for the use of bisphosphonates (BPs) in multiple myeloma.¹ Although the IMWG is in general agreement with the Mayo consensus statement, several important issues have been raised and are discussed subsequently. These comments are in response to the recommendations of the Mayo group, which is normally part of the IMWG.

Recommendations for Using BP in Myeloma.

Starting BP Therapy. It is agreed that pretreatment dental evaluation is important in patients who will be treated with intravenous BP.²

Bisphosphonate therapy is appropriate for patients with overt lytic bone disease on radiographs.

Most investigators favor the use of other imaging studies in addition to radiographs to clarify the exact status of myeloma-related bone disease as a basis for the decision to initiate BP therapy and to monitor bone disease serially. Magnetic resonance imaging with gadolinium enhancement (confirmable with computed tomography if necessary) and/or whole-body computed tomography/positron emission tomography (if available) can be used to identify focal bone destruction.³ Emphasis is placed on direct documentation of myeloma-related bone destruction or loss.

The role of bone density testing is complex. Currently, it is not widely used in patients with myeloma. Nonetheless, those who do not use it concede and those who do use it emphasize its potential importance and utility both at baseline and for monitoring. Bone loss, increasing age, female sex, and planned high-dose corticosteroid use predict increased fracture risk and the potential need for oral or intravenous BP therapy. Other monitoring tools include N-telopeptide and/or deoxypyridinoline measurements, which can indicate enhanced bone turnover.

Even when all bone test results are inconclusive, some investigators still recommend intravenous BP therapy for this small subset of patients without definite bone disease but with documented active myeloma. However, BP use is not recommended in patients with smoldering myeloma.

Duration of BP Therapy. We concur that BP use should no longer be indefinite or open ended.

We agree that the duration of BP therapy should be modified on the basis of evidence of ongoing active bone disease.

In patients who have achieved a complete response or a very good partial response with transplantation and/or a novel therapy combination and have no active bone disease, BP therapy is not recommended beyond the first year. This recommendation is based on results from the Inter-Groupe Francophone du Myelome trial, which showed no delay in time to onset of bone events with ongoing BP use.⁴

For patients achieving less than a very good partial response and/or those with ongoing active bone disease, further BP use is recommended. After 2 years, patients without active bone disease can discontinue BP use. Because no data indicating the value of a reduced-frequency (and/or reduced-dose) schedule are available, stopping BP treatment at 2 years is recommended, rather than the Mayo recommendation to decrease BP use to a schedule of periodic treatment such as every 3 months.

For patients with continued active bone disease after 2 years of BP therapy, further BP use is recommended at the discretion of the primary physician. Pamidronate or clodronate is preferred for longer-term use (>2 years).

In patients who experience relapse with new bone disease, BP therapy, using pamidronate or clodronate if available, should be reinstated.

Careful monitoring of renal function, including serum creatinine and periodic urinary protein measurements, is required with long-term BP use.

As noted by the Mayo Clinic team, osteonecrosis of the jaw (ONJ) is the major new concern with long-term BP use.⁵⁻⁸ Use of pamidronate or clodronate has the lowest risk, especially with treatment duration of 1 or 2 years and the recommended dental precautions. The risk of ONJ with pamidronate is 1% to 2% within the first 2 years of treatment, and the risk associated with clodronate is 0% to 0.5% (only rare cases have been reported). The risk with zoledronic acid is approximately 2-fold higher than that with pamidronate.⁵⁻⁸ Oral nitrogen-containing BPs have been associated with ONJ⁵⁻⁸ and thus are not currently recommended as an alternative to clodronate.

Patients who develop ONJ should discontinue BP therapy.

Choice of BP Therapy. There is nearly unanimous consensus that pamidronate has equivalent efficacy compared to other BPs plus a favorable toxicity profile. Thus, in general, investigators favor pamidronate over zoledronic acid, as did the Mayo team.¹

Outside the United States, clodronate is a widely available oral alternative that is considered an equally safe option.⁹⁻¹¹

Zoledronic acid is the primary choice of a few experts (13%), based on the convenience of the shorter infusion time but also because of the possible added clinical benefits of reduction in bone events and/or improved survival compared with other BPs. Ongoing further studies of zoledronic acid are needed to assess schedules and infusion times, which may reduce the risk of complications and/or enhance outcomes.

Dental Evaluation. Consensus exists concerning the need for dental evaluation. The scope of baseline and serial evaluation depends on local details within the health care system as well as personal resources. Physicians should emphasize to their patients the need to avoid dental procedures such as extractions while they are receiving BP therapy.

Conclusion. As noted recently,¹² the preparation of good guidelines is a complex process. We hope that the added details provided herein will enhance the Mayo consensus statement.

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