



# A Canadian Perspective on the Use of Bisphosphonates in the Clinical Management of Multiple Myeloma

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## Background

Multiple myeloma (MM) represents approximately 1% of all reported cancers worldwide and 12%–15% of hematological malignancies.<sup>1</sup> In Canada, the average age at diagnosis is 62 years for men and 61 years for women, with only 4% of cases diagnosed in patients under 45.<sup>2</sup> Incidence rates are 5/100,000, with higher rates in men than in women (6/100,000 vs. 4/100,000).<sup>3</sup> Despite advances in the treatment of MM, the disease remains largely incurable, with an annual death rate of 4.1/100,000 and a five-year survival rate of 28%.<sup>4</sup> Improving survival in MM therefore remains the primary goal of treatment.<sup>5</sup>

Patients commonly present with lytic bone disease, hypercalcemia, immunodeficiency, renal insufficiency, and anemia resulting from clonal expansion of plasma cells.<sup>4</sup> Destruction of bone occurs in approximately 79% of patients with MM and can result in significant bone pain, pathological fractures, spinal cord compression, hypercalcemia, and other skeletal-related events (SREs).<sup>4,6</sup>

The most common osteolytic lesions include the vertebrae, ribs, skull, femur, hip, and humerus, but in approximately 15% of patients, diffuse osteopenia is the only bone manifestation.<sup>7</sup> A number of these skeletal complications are associated with significant morbidity and can have a negative impact on survival, mobility, day-to-day independence, and quality of life (QoL), as well as increase treatment costs.<sup>4</sup> Given the primary goal to improve survival in patients with MM, appropriate treatment with supportive care is of paramount importance.

Preclinical studies suggest newer MM therapies, such as thalidomide, bortezomib, and lenalidomide, decrease bone resorption, principally by reducing tumour burden; these therapies may also have a direct effect on bone turnover. However, further research is needed to determine whether these agents can successfully reduce SREs.<sup>8</sup> Bisphosphonates are therefore the current standard of care to reduce and delay the skeletal morbidity caused by MM.<sup>4</sup>

Bisphosphonates are synthetic, stable analogues of inorganic pyrophosphate, which are found in the bone matrix. They have an affinity for bone and are preferentially delivered to sites of increased bone formation or resorption. Once deposited, bisphosphonates are internalized by osteoclasts that are engaged in bone resorption and modulate signalling from osteoblasts to osteoclasts. As potent inhibitors of osteoclast-induced bone resorption, bisphosphonates are effective at preventing, reducing, and delaying SREs related to MM.<sup>4,9</sup>

There are two major classes of bisphosphonates: nitrogen-containing and non-nitrogen-containing. Non-nitrogen-containing bisphosphonates, such as clodronate (CLO), form non-hydrolyzable toxic adenosine triphosphate (ATP) analogues that inhibit ATP-dependent intracellular enzymes and induce apoptosis. Nitrogen-containing bisphosphonates, such as pamidronate (PAM) and zoledronic acid (ZOL), inhibit farnesyl pyrophosphate synthase (FPPS), a key enzyme in the mevalonate pathway and an important mediator of osteoclast function and survival. Nitrogen-containing bisphosphonates have a unique mechanism of action and greater clinical activity than first-generation bisphosphonates. Of the second-generation bisphosphonates, ZOL is the most potent.<sup>10</sup> ZOL, CLO, and PAM are all available in Canada, but reimbursement criteria differ across provinces and territories.

### Purpose of this document

Currently, no uniform standard of care exists across Canada for the use of bisphosphonates in MM. Although a number of guidelines have been established worldwide, no Canadian recommendations have been developed for the use of bisphosphonates in these patients.

Dr. Donna Reece, Dr. Michael Sebag, Dr. Darrell White, and Dr. Kevin Song drafted this document, which presents a Canadian perspective on the use of bisphosphonates in MM. Topics addressed include diagnosis of bone disease; bisphosphonates and their relationship to SREs, bone pain, hypercalcemia, and overall survival (OS); and optimal duration of bisphosphonate treatment. In a separate document entitled *A Canadian Perspective on the Management of Bisphosphonate-Related Complications in Multiple Myeloma*, topics such as appropriate monitoring and the management of treatment-related complications are discussed.

The following paper describes a general consensus on the use of bisphosphonates in MM, but does not reflect a true evidence-based guideline process with a systematic literature review. In addition, patient preference should always be considered in any treatment decision.

## Skeletal Complications

### Assessment

#### Imaging studies

The standard diagnostic procedure for the detection of skeletal complications in MM is conventional radiography. A standard skeletal survey should include a postero-anterior (PA) view of the chest; antero-posterior (AP) and lateral views of the cervical spine, thoracic spine, lumbar spine, humeri, and femora; AP and lateral view of the skull; and AP view of the pelvis. Other symptomatic areas should be visualized using the appropriate views.<sup>11</sup>

Despite the advantages of radiography, bone destruction can occur in the absence of osteolytic lesions on skeletal radiography, suggesting diagnostic sensitivity is low in early stage disease. Studies have found that a loss of 30%–50% of the trabecular bone is required for detection of lytic lesions using this diagnostic method.<sup>7</sup> Computed tomography (CT) scanning or magnetic resonance imaging (MRI) should therefore be used to clarify ambiguous findings, such as equivocal lytic lesions, especially in areas difficult to visualize, such as the ribs, sternum, and scapulae.<sup>11</sup> When cord compression is suspected, MRI is the technique of choice. In patients with symptomatic MM, the number of focal lesions detected by MRI has been shown to be an independent prognostic factor for survival.<sup>7,11</sup>

However, bone scans typically underestimate myeloma bone lesions.<sup>4</sup> In addition, evidence is insufficient to recommend positron-emission tomography (PET) or <sup>99m</sup>Tc sestamibi (MIBI) imaging for the assessment of bone disease.<sup>11</sup> Despite the existence of other promising imaging tests, the skeletal survey remains the recommended imaging modality at diagnosis.

#### Bone biomarkers

Biochemical markers of bone resorption, such as amino- and carboxy-terminal cross-linking telopeptide of type I collagen (NTX and CTX) and CTX generated by matrix metalloproteinases (ICTP), and bone formation are being evaluated in MM, but are not yet in routine use.<sup>7</sup> Bone resorption and bone formation markers provide information on bone metabolism and reflect disease activity in bone. Bone biomarkers are useful in assessing the extent of bone destruction, risk of

skeletal morbidity, and response to bisphosphonates. High levels of urinary NTX, serum CTX, and serum ICTP suggest advanced disease in MM patients with osteolytic lesions. In addition, high levels of urinary NTX and serum ICTP are associated with increased risk of SREs, disease progression, and OS. Bone markers have also been used for the early diagnosis of bone lesions.<sup>8</sup>

Measurement of bone turnover markers is non-invasive, relatively inexpensive, and can be useful in the assessment of bone disorders when applied and interpreted correctly. However, factors that influence bone biomarker levels, including circadian rhythm, diet, age, gender, renal function, and drugs need to be taken into account. In addition, these markers reflect whole-body bone turnover and give little information about the function of local changes in skeletal homeostasis. Given the above methodological difficulties, routine use of bone biomarkers is not currently recommended.<sup>8</sup>

#### Novel anti-myeloma agents

During the last decade, immunomodulatory drugs, including thalidomide and lenalidomide, and proteasome inhibitors, such as bortezomib, have significantly contributed to the improved OS of patients with MM. Thalidomide, lenalidomide, and bortezomib have proven to be effective agents for the treatment of both newly diagnosed and relapsed/refractory MM.<sup>12</sup>

Some data suggest these MM therapies may also reduce bone destruction, presenting a possible alternative to standard bisphosphonate therapy. The role of these agents in bone metabolism has been evaluated in several studies, which are described in Table 1.<sup>8</sup> However, clinically meaningful results have not been demonstrated with respect to the usefulness of these agents in reducing fractures, spinal cord compressions, or the need for surgery to bone. Use of these therapies to prevent bone destruction in MM is therefore premature and awaits the results of future research. Given the possible influence of these agents on bone metabolism, it is important to consider their impact when evaluating the efficacy of bisphosphonates.

**Table 1. Effect of anti-myeloma agents on bone biomarkers<sup>8</sup>**

Agent	MM study population	N	Results	Subpopulation analysis
<i>Thalidomide (+ dexamethasone)</i>				
Tosi, et al.*	Newly diagnosed	40	↓ Bone resorption markers (CTX, NTX)	In responders
			↓ Bone formation markers (BALP, OC)	In all patients
Terpos, et al.*	Refractory/relapsed	35	↓ Bone resorption markers (CTX, TRACP-5b)	In all patients
			↓ Osteoclast stimulators (sRANKL, sRANKL/OPG ratio)	In all patients
			↔ Bone formation markers (BALP, OC)	In all patients
<i>Lenalidomide</i>				
Breitkreutz, et al.	Refractory/relapsed	11	↓ Osteoclast numbers	NA
			↓ Osteoclast differentiation	NA
			↓ Bone resorption	NA
<i>Bortezomib (± dexamethasone)</i>				
Heider, et al.*	Refractory/relapsed	58	↑ Bone formation markers (BALP, OC)	In all patients
Terpos, et al.*	Refractory/relapsed	34	↓ Bone resorption markers (CTX, TRACP-5b)	In all patients
			↓ Osteoclast stimulators (sRANKL, sRANKL/OPG ratio)	In all patients
			↑ Bone formation markers (BALP, OC)	In responders <sup>†</sup>
			↓ Osteoblast inhibitors (Dkk-1)	In all patients
Giuliani, et al.*	Refractory/relapsed	21	↓ Bone resorption markers (CTX)	In all patients <sup>‡</sup>
			↑ Osteoclast numbers	In responders
Terpos, et al.* (VMDT regimen)	Refractory/relapsed	62	↓ Bone resorption markers (CTX, TRACP-5b)	In all patients
			↓ Osteoclast stimulators (sRANKL, sRANKL/OPG, MIP-1 alpha)	In all patients
			↔ Bone formation markers (BALP, OC)	In all patients
			↓ Osteoblast inhibitors (Dkk-1)	In all patients

Adapted from Terpos E, et al. *Leukemia* 2010.

\*Concomitant bisphosphonates administration in the majority of patients.

<sup>†</sup>BALP was increased only in responders, while OC was elevated in all patients.

<sup>‡</sup>This reduction did not reach statistical significance.

BALP = bone-specific alkaline phosphatase; CTX = carboxy-terminal cross-linking telopeptide of type I collagen; DKK-1 = dickkopf-1; MIP-1 alpha = macrophage inflammatory protein-1 alpha; MM = multiple myeloma; NA = not applicable; NTX = amino-terminal cross-linking telopeptide of type I collagen; OC = osteocalcin; OPG = osteoprotegerin; sRANKL = soluble form receptor activator of nuclear factor-KB ligand; TRACP-5b = tartrate-resistant acid phosphatase isoform type 5b; VMDT = bortezomib, melphalan, dexamethasone, and thalidomide

## Bisphosphonates

Quality of life in patients with MM is often compromised by pain, fatigue, and deteriorating physical function, with accompanying emotional and psychological difficulties and disrupted role functioning.<sup>13</sup> A review of 1,027 patients diagnosed with MM at the Mayo Clinic between the years 1985 and 1998 showed that bone pain was present in 58% of patients at diagnosis. Conventional radiographs at diagnosis showed lytic lesions, osteoporosis, or fractures in 79% of patients.<sup>6</sup> Bone pain is associated with significant morbidity and has a negative impact on activities of daily living. When the spine or lower limbs are involved, mobility may be impeded, significantly reducing patient QoL.<sup>14</sup>

The first bisphosphonate tested in a clinical setting was etidronate (ETI), a weak bisphosphonate, which showed no benefit in reducing SREs, bone pain, or fracture in MM patients.<sup>15–18</sup> However, subsequent randomized studies using CLO, a bisphosphonate that is 10 times more potent than ETI, found significant reductions in the development of osteolytic lesions, bone pain, fracture rate, and the time to first non-vertebral fracture.<sup>18–22</sup>

PAM, a second-generation bisphosphonate, is 100-fold more potent than ETI and can be given orally or intravenously. A preliminary randomized study using oral PAM found no reduction in SREs, which the investigators attributed to low absorption of the oral formulation.<sup>17,18,23</sup> Subsequently, a randomized study using IV PAM found a reduced number of SREs and time to first skeletal event. An extension of this study to a total of 21 cycles of PAM confirmed earlier results of a reduction in SREs with IV PAM.<sup>24,25</sup>

ZOL is 100 to 850 times more potent than PAM. A phase II trial comparing ZOL and PAM showed that both bisphosphonates significantly reduced SREs, and a large, phase III trial showed an increase in time to first SRE in both groups.<sup>17,18,26–28</sup> However, the skeletal morbidity rate and normalization of the bone resorption marker NTX were improved in the ZOL group.<sup>27</sup> A follow-up study showed that ZOL was more effective than PAM in reducing the risk of skeletal complications in patients with bone metastases from breast carcinoma by an additional 20% ( $p = 0.025$ ). Efficacy of ZOL and PAM were similar in MM patients.<sup>28</sup> Studies examining the effect of bisphosphonates on SREs are presented in Table 2.<sup>15,16,19–23,25–41</sup>

A recent Cochrane analysis by Mhaskar, *et al.* (2010) analyzed data from 17 trials, with 1,520 patients in bisphosphonate

groups, and 1,490 in control groups. A total of seven studies were included in the pooled analysis examining the effect of bisphosphonates on SREs (1,497 patients) and vertebral fractures (1,116 patients). In comparison with placebo/no treatment, the pooled analysis demonstrated an overall beneficial effect of bisphosphonates for the prevention of pathological vertebral fractures (RR 0.74, 95% CI: 0.62–0.89;  $p = 0.001$ ) and total SREs (RR 0.80, 95% CI: 0.72–0.89;  $p < 0.0001$ ). However, the analysis found no benefit of one bisphosphonate over another for most comparisons.<sup>43</sup>

The Myeloma IX trial, a recently published randomized study by the UK Medical Research Council (MRC), compared ZOL and CLO with a median follow-up of 3.7 years. Groups were well balanced, with similar numbers of patients randomized to treatment with ZOL versus CLO ( $n = 981$  vs. 979). Numbers of patients in the ZOL and CLO groups randomized to intensive therapy ( $n = 555$  vs. 556) and non-intensive therapy ( $n = 426$  vs. 423) were also well balanced. Results of the Myeloma IX trial showed significant benefits of ZOL over CLO in the reduction of SREs (27% vs. 35%;  $p = 0.0004$ ).<sup>40,44</sup> An updated Cochrane analysis by Mhaskar, *et al.* incorporated data from the Myeloma IX trial into the 2010 analysis to determine whether this study would influence results. Preliminary results of the updated analysis presented at ASH 2010 showed ZOL to be superior to CLO and PAM in the prevention of SREs in patients with MM.<sup>45</sup>

Results of clinical trials suggest bisphosphonates are effective at preventing, reducing, and delaying SREs related to MM. In addition, results of studies comparing ZOL to other bisphosphonates suggest ZOL may be superior to other agents for reducing skeletal complications associated with MM.

There is little evidence to support the use of bisphosphonates in asymptomatic patients with MM. A trial of monthly intravenous PAM versus placebo in newly diagnosed patients not requiring chemotherapy found a reduction in SREs; however, time to disease progression was not reduced.<sup>34</sup> Use of bisphosphonates in asymptomatic patients is therefore not recommended by existing guideline committees, except as part of clinical trials.

Recommendations from existing guidelines on the use of bisphosphonates in MM are presented in Table 3.<sup>4,9,11,46–51</sup>

**Table 2. Reduction in skeletal-related events with the use of bisphosphonates in multiple myeloma**

Author and year	BP	Dosage	MM patients (n)	Reduction of SREs*	Reduction in pain
Delmas, et al. (1982) <sup>29</sup>	CLO	1600 mg/day, PO	13	Yes	Yes
Belch, et al. (1991) <sup>15</sup>	ETI	5 mg/kg/day, PO	173	No	No
Lahtinen, et al. (1992) <sup>19</sup> Laakso, et al. (1994) <sup>20</sup>	CLO	2400 mg/day, PO for 24 months	350	Yes	Yes
Daragon, et al (1993) <sup>16</sup>	ETI	10 mg/kg/day, PO for 4 months	94	No	No
Heim, et al. (1995) <sup>30</sup>	CLO	1600 mg/day, PO	170	Yes	Yes
Berenson, et al. (1996) <sup>31</sup> Berenson, et al. (1998) <sup>25</sup>	PAM	90 mg, IV every 4 weeks for 21 cycles	392	Yes	Yes
McCloskey, et al (1998) <sup>21</sup> McCloskey, et al (2001) <sup>22</sup>	CLO	1600 mg/day, PO	536	Yes	Yes
Brincker, et al. (1998) <sup>23</sup>	PAM	300 mg/day, PO	300	No	Yes
Kraj, et al. (2000) <sup>32</sup>	PAM	60 mg, IV every 4 weeks	46	Yes	Yes
Terpos, et al. (2000) <sup>33</sup>	PAM	90 mg, IV every 4 weeks	62	No	Yes
Berenson, et al. (2001) <sup>†,26</sup>	ZOL PAM	ZOL: 0.4, 2, or 4 mg, IV or PAM: 90 mg, IV every 4 weeks for up to 10 months	108	Yes (ZOL non-inferior to PAM)	Yes
Rosen, et al. (2001) <sup>27</sup> Rosen, et al. (2003) <sup>†,28</sup>	ZOL PAM	ZOL: 4 or 8 mg, IV or PAM: 90 mg, IV every 3–4 weeks for 24 months	353	Yes (ZOL>PAM)	Yes
Leng, et al. (2002) <sup>42</sup>	PAM	90 mg, IV daily	34	NE	Yes
Musto, et al. (2003) <sup>34</sup>	PAM	60 mg, IV every 4 weeks	90	Yes	NE
Attal, et al. (2006) <sup>35</sup>	PAM	90 mg, IV every 4 weeks	597	No	NE
Avilés, et al. (2007) <sup>36</sup>	ZOL	4 mg, IV every 28 days	94	Yes	NE
Musto, et al. (2008) <sup>37</sup>	ZOL	4 mg, IV every month	163	Yes	NE
Henk, et al. (ASH 2009) <sup>38</sup>	ZOL	All dose variations	1655	Yes	NE
Gimsing, et al. (2010) <sup>39</sup>	PAM	30 or 90 mg, IV every month for at least 3 years	504	No (difference between doses)	NE
Morgan, et al. (2010) <sup>‡,40</sup>	ZOL CLO	ZOL: 4 mg, IV every 3–4 weeks or CLO: 1600 mg/day, PO	1960	Yes (ZOL>CLO)	NE
Sezer, et al. (2010) <sup>41</sup>	ZOL	4 mg, IV every 4 weeks	140	NS trend	NE

\* SREs include new lytic lesions, vertebral and non-vertebral fractures, and need for radiation or surgery to the bone.

† PAM-controlled trial.

‡ CLO-controlled trial.

BP = bisphosphonate; CLO = clodronate; ETI = etidronate; IV = intravenous; MM = multiple myeloma; NE = not examined; NS = non-significant; PAM = pamidronate; PO = oral; SRE = skeletal-related event; ZOL = zoledronic acid

Table 3. Summary of recommendations for bisphosphonate use in multiple myeloma		
Guideline	Year	Recommendations
BCSH/UKMF <sup>11</sup>	2010	<ul style="list-style-type: none"> <li>• BP therapy is recommended for all patients with symptomatic MM, regardless of whether bone lesions are evident.</li> <li>• ZOL and PAM both show efficacy in regards to SREs, but data from the Myeloma IX study showing an EFS and OS benefit of ZOL suggest ZOL should be the treatment of choice.</li> <li>• All patients with moderate-to-severe hypercalcemia should receive a BP; ZOL is the treatment of choice.</li> </ul>
NCCN <sup>46</sup>	2010	<ul style="list-style-type: none"> <li>• BP therapy is recommended for all patients with MM who have bone disease, including osteopenia; PAM is favoured over ZOL due to risk of ONJ.</li> <li>• In smoldering or stage I disease, BPs should preferably be used in the context of a clinical trial. These patients should have a bone survey yearly.</li> <li>• BP therapy is recommended for hypercalcemia.</li> </ul>
EMN <sup>4</sup>	2009	<ul style="list-style-type: none"> <li>• BP therapy is recommended for all MM patients: <ul style="list-style-type: none"> <li>– with lytic bone disease on plain radiographs;</li> <li>– with osteopenia or osteoporosis on BMD studies;</li> <li>– on chemotherapy.</li> </ul> </li> <li>• ZOL, CLO, or PAM should be used as indicated.</li> </ul>
BCCA <sup>47</sup>	2008	<ul style="list-style-type: none"> <li>• Intravenous PAM should be given to all patients receiving chemotherapy for myeloma.</li> </ul>
ASCO <sup>48</sup>	2007	<ul style="list-style-type: none"> <li>• BP therapy is recommended for MM patients: <ul style="list-style-type: none"> <li>– with lytic bone disease on plain radiographs or imaging studies;</li> <li>– with osteopenia based on normal plain radiograph or BMD measurements.</li> </ul> </li> <li>• PAM is favoured over ZOL due to risk of ONJ.</li> </ul>
CCO <sup>49</sup>	2007	<ul style="list-style-type: none"> <li>• BP therapy is recommended for all MM patients who have lytic bone lesions, osteopenia, or osteoporosis.</li> <li>• Patients who do not have lytic lesions, osteopenia, or osteoporosis should be informed of the potential benefits and risks of therapy and offered BP treatment.</li> <li>• Oral CLO and IV PAM or ZOL are reasonable choices. Patient preference, tolerance, and convenience will influence choice.</li> </ul>
IMWG Reply to Mayo <sup>50</sup>	2007	<ul style="list-style-type: none"> <li>• Other imaging studies such as MRI, CT, and CT/PET recommended in addition to radiographs as basis for decision to initiate BP therapy.</li> <li>• PAM generally favoured over ZOL due to risk of ONJ, but experts noted the shorter infusion time and possible survival benefits of ZOL and were awaiting further studies.</li> </ul>
Mayo <sup>9</sup>	2006	<ul style="list-style-type: none"> <li>• BP therapy is recommended for MM patients: <ul style="list-style-type: none"> <li>– with lytic bone disease on plain radiographs;</li> <li>– with osteopenia or osteoporosis on BMD studies.</li> </ul> </li> <li>• PAM is favoured over ZOL in patients with newly diagnosed MM due to risk of ONJ, but guidelines do not necessarily advocate switching patients already on ZOL to PAM.</li> </ul>
ESMO <sup>51</sup>	2005	<ul style="list-style-type: none"> <li>• BP therapy recommended for patients with stage III or relapsed MM receiving conventional-dose chemotherapy.</li> </ul>

ASCO = American Society of Clinical Oncology; BCCA = British Columbia Cancer Agency; BCSH/UKMF = British Committee for Standards in Hematology/United Kingdom Myeloma Forum; CCO = Cancer Care Ontario; EMN = European Myeloma Network; ESMO = European Society for Medical Oncology; IMWG = International Myeloma Working Group; Mayo = Mayo Clinic; NCCN = National Comprehensive Cancer Network

BMD = bone mineral density; BP = bisphosphonate; CLO = clodronate; CT = computed tomography; EFS = event-free survival; MM = multiple myeloma; MRI = magnetic resonance imaging; ONJ = osteonecrosis of the jaw; OS = overall survival; PAM = pamidronate; PET = positron emission tomography; SRE = skeletal-related event; ZOL = zoledronic acid

## Recommendations

Based on the evidence to date, the following is recommended for the assessment and treatment of skeletal complications in multiple myeloma:

- Currently, a skeletal survey is recommended for assessment of bone destruction in all patients with multiple myeloma.
- Additional imaging modalities should be considered in specific clinical situations, such as in patients with cord compression (MRI) or plasmacytomas (MRI/CT scan).
- Usefulness of new multiple myeloma treatments in the absence of bisphosphonates to prevent bone destruction awaits the results of future studies.
- All patients can be considered candidates for bisphosphonates, regardless of whether bone lesions are evident.
- The strength of the results of studies examining skeletal-related event outcomes with zoledronic acid, and findings from the recent Myeloma IX trial and the updated Cochrane analysis, suggest zoledronic acid may be the bisphosphonate of choice for reducing skeletal-related events in multiple myeloma.

## Bone Pain

Pain is one of the most common symptoms of MM and is reported in up to 67% of patients at diagnosis. At diagnosis, pain may arise due to disease processes, such as destructive bone disease, or occasionally from plasmacytomas that directly affect neural tissues. Pain may also signify the presence of co-morbidities, such as degenerative arthritis or osteoporosis. Later in the disease course, pain often arises as a side effect of therapies, such as neuropathy associated with bortezomib treatment.<sup>14</sup>

Results of clinical trials show bisphosphonates are able to reduce bone pain and maintain the pain at a lower level.<sup>4,21,24</sup> (Table 2) Evidence also suggests that bisphosphonates improve patient QoL and reduce analgesic consumption. However, the improvement in pain with bisphosphonates could be the result of a decrease in disease burden and may therefore reflect

an indirect relationship.<sup>4</sup> Randomized studies using CLO and PAM have demonstrated a significant reduction in bone pain as well as improvements in QoL, compared to placebo.<sup>21,24</sup> In addition, the 2010 Cochrane analysis by Mhaskar, *et al.* pooled data from a total of eight studies (1,281 patients) examining the impact of bisphosphonates on pain compared to placebo/no treatment. Results of the pooled analysis demonstrated an overall amelioration of pain with bisphosphonates compared to placebo/no treatment (RR 0.75, 95% CI: 0.60 to 0.95;  $p = 0.01$ ). However, there was no benefit of one bisphosphonate over another for most comparisons.<sup>43</sup>

Adding bisphosphonates to other pain management strategies, such as pharmacological treatments, radiotherapy, and psychological techniques, is therefore a reasonable option in patients with MM.

## Recommendation

Based on the evidence to date, the following is recommended for the use of bisphosphonates in the management of bone pain in multiple myeloma:

- Pain arising in myeloma patients should be managed using a multi-modal approach that may include the addition of bisphosphonates as appropriate.

## Overall Survival

Although novel therapies have resulted in improvements in response rates, time to progression, and survival, MM is still an incurable disease. The primary treatment goal remains the improvement of survival.<sup>5</sup> Preclinical studies suggest that second generation bisphosphonates have anti-cancer properties beyond the prevention of bone destruction.<sup>52</sup> In addition, evidence from a recent randomized clinical trial shows ZOL improves survival in patients with MM.<sup>40</sup>

### Preclinical studies

Results of in vitro and in vivo studies suggest nitrogen-containing bisphosphonates (N-BPs) have important anti-tumour effects against myeloma cells.<sup>43</sup> In vitro studies show that N-BPs induce the proliferation of  $\gamma\delta$ T cells and act as cytotoxic agents against myeloma cells. Stimulation of  $\gamma\delta$ T cells results in a pronounced effect on the immune system, which may partly explain the anti-tumour effect of these agents.<sup>4</sup> Studies in animal models have shown a relationship between myeloma cells and osteoclast activity.<sup>53</sup> In addition, some evidence suggests that ZOL reduces tumour burden in bone and prevents osteolytic bone disease in mice.<sup>4,54,55</sup> Results of PAM-based studies have also shown anti-myeloma activity in these animal models.<sup>4,56,57</sup>

Recent animal studies suggest a potential anti-cancer effect of ZOL that is independent of osteoclast activity.<sup>52,58</sup> Results of these studies suggest that ZOL interferes with a number of steps in the metastatic cascade, including tumour cell proliferation, adhesion and invasion, and angiogenesis.<sup>52,59</sup>

Given the results of in vitro and animal studies showing a possible anti-tumour effect of N-BPs, it is important to determine whether these agents are capable of improving survival in patients with MM.

### Clinical trials

Bisphosphonates have been a mainstay supportive care treatment for bone disease in patients with MM for over a decade. Evidence of ZOL's anti-cancer activity has been shown in a number of studies across a broad range of malignancies.<sup>60-64</sup> Recent evidence demonstrates that bisphosphonates may also have an important role to play in delaying disease progression and improving survival in patients with MM. (Table 4)<sup>15,16,21-23,25,27,28,31,35,36,38,40,44,65</sup>

PAM was the first bisphosphonate to show a trend to improved survival in a subgroup of patients. In a study by Berenson, *et al.* (1998), survival in patients with more advanced disease was significantly increased in the PAM group (median survival 21 months vs. 14 months;  $p = 0.041$ , after adjusting for baseline serum,  $\beta_2$ -microglobulin, and Eastern Cooperative

Oncology Group [ECOG] performance status).<sup>25,43</sup> An oral form of PAM, however, showed no survival benefit.<sup>23</sup>

The impact of CLO on survival was also tested in a number of randomized trials. In a study by Lahtinen, *et al.* (1992), the proportion of patients who experienced a progression of lytic lesions was smaller in the CLO-treated group than in the placebo group. However, no significant effect on survival was seen.<sup>19</sup> In an open label study by Heim, *et al.* (1995), there was a trend toward reduction in the number of new bone lesions in the CLO group. Again, no significant effect on survival was seen.<sup>30</sup> Finally, a study by McCloskey, *et al.* (1998) concluded that there was no difference in OS for MM patients treated with CLO. However, in a post hoc analysis, patients without vertebral fracture at study entry survived significantly longer on CLO than on placebo (median survival 59 months vs. 37 months,  $p = 0.004$ ).<sup>21,22</sup>

Studies examining survival outcomes with ZOL have been promising. A study by Rosen, *et al.* (2001 and 2003) compared ZOL to PAM in patients with bone lesions secondary to advanced breast carcinoma or MM.<sup>27,28</sup> An exploratory, retrospective analysis using data from the Rosen study of a subset of MM patients who had information on baseline bone-specific alkaline phosphatase (BALP) levels showed that the OS rate at 25 months was significantly higher in ZOL-treated patients than in those treated with PAM (76% vs. 63%;  $p = 0.026$ , Cox regression). Among patients with low BALP levels, the survival rates were similar for both treatment groups. However, among patients with high baseline BALP levels, ZOL treatment significantly improved survival at study end compared with PAM (82% vs. 53%;  $p = 0.041$ , log-rank test).<sup>65</sup> Subsequently, a randomized study comparing ZOL to no therapy showed an OS benefit of ZOL, with five-year OS rates of 80% and 46% for ZOL and placebo, respectively.<sup>36</sup> Studies examining the effect of bisphosphonates on survival are presented in Table 4.

Results from CLO and PAM trials suggest some survival benefit from these agents, but improvements were limited to subgroup analyses. (Table 4) The 2010 Cochrane analysis by Mhaskar, *et al.* pooled data from a total of eleven studies (2,221 patients) examining the impact of bisphosphonates on mortality, compared to placebo/no treatment. Results of the pooled analysis also showed no reduction in the risk of mortality with bisphosphonates versus placebo/no treatment (HR 0.96, 95% CI: 0.80-1.14;  $p = 0.64$ ). No difference in survival outcomes were found between bisphosphonates.<sup>43,66</sup>

**Table 4. Improvement in survival with the use of bisphosphonates in multiple myeloma**

Author and year	BP	Dosage	MM patients (n)	Survival benefit
Belch, et al. (1991) <sup>15</sup>	ETI	5 mg/kg/day, PO	173	No
Daragon, et al (1993) <sup>16</sup>	ETI	10 mg/kg/day, PO for 4 months	94	No
Berenson, et al. (1996) <sup>31</sup> Berenson, et al. (1998) <sup>25</sup>	PAM	90 mg, IV every 4 weeks for 21 cycles	392	Subset*
McCloskey, et al (1998) <sup>21</sup> McCloskey, et al (2001) <sup>22</sup>	CLO	1600 mg/day, PO	536	Subset†
Brincker, et al. (1998) <sup>23</sup>	PAM	300 mg/day, PO	300	No
Rosen, et al. (2001) <sup>27</sup> Rosen, et al. (2003) <sup>‡,28</sup>	ZOL PAM	ZOL: 4 or 8 mg, IV or PAM: 90 mg, IV every 3–4 weeks for 24 months	353	Subset§
Attal, et al. (2006) <sup>35</sup>	PAM	90 mg, IV every 4 weeks	597	No
Berenson, et al. (ASH 2006) <sup>65</sup>	ZOL PAM	ZOL: 4 or 8 mg, IV or PAM: 90 mg, IV every 3–4 weeks for 24 months	353	Subset§
Avilés, et al. (2007) <sup>36</sup>	ZOL	4 mg, IV every 28 days	94	Yes
Henk, et al. (ASH 2009) <sup>38</sup>	ZOL	All dose variations	1655	Yes
Morgan, et al. (2010) <sup>¶,40,44</sup>	ZOL CLO	ZOL: 4 mg, IV every 3–4 weeks or CLO: 1600 mg/day, PO	1960	Yes

\* Survival in patients with more advanced disease was significantly increased in the PAM group compared to placebo (median survival 21 months vs. 14 months;  $p = 0.041$  adjusted for baseline serum,  $\beta_2$ -microglobulin, and Eastern Cooperative Oncology Group [ECOG] performance status).

† In post hoc analysis, patients without vertebral fracture at study entry survived significantly longer on CLO than on placebo (median survival 59 months versus 37 months,  $p = 0.004$ ).

‡ PAM-controlled trial.

§ Survival benefit with ZOL over PAM in a subgroup of patients who had elevated baseline BALP levels.

¶ CLO-controlled trial.

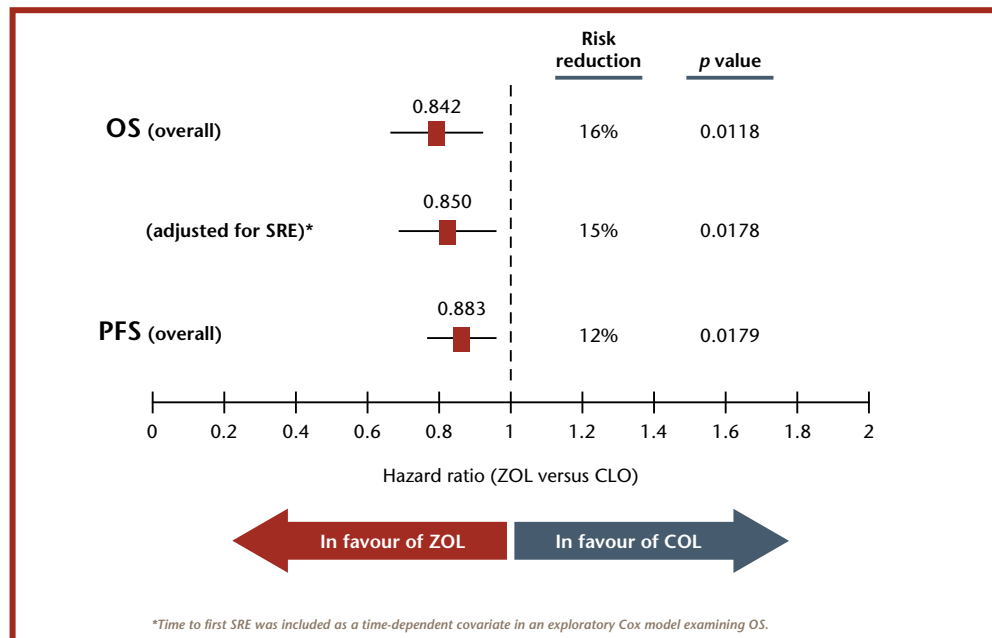
BP = bisphosphonate; CLO = clodronate; ETI = etidronate; IV = intravenous; MM = multiple myeloma; PAM = pamidronate; PO = oral; ZOL = zoledronic acid

Recently, the Myeloma IX trial reported that after a median follow-up of 3.7 years, a significant benefit of ZOL over CLO was found for OS (50 months vs. 44.5 months,  $p = 0.04$ ) and for overall progression-free survival (PFS) (HR 0.88;  $p = 0.0179$ ). A trend for increased median PFS with ZOL (19.5 months vs. 17.5 months,  $p = 0.07$ ) was also seen.<sup>40,44</sup> (Figure 1) ZOL reduced mortality by 16% (95% CI: 4–26) versus CLO (HR 0.84, 95% CI: 0.74–0.96;  $p = 0.0118$ ). For non-intensive therapy, ZOL had a significantly increased rate of complete response (CR) or very good partial response (VGPR), compared to CLO ( $p = 0.018$ ). Moreover, ZOL improved OS independently of the reduction in SREs, suggesting that the drug has underlying anti-myeloma effects, which is consistent with the higher CR and VGPR rates. The Myeloma IX trial was the first study to show a survival advantage of one bisphosphonate over another. Results also showed that OS benefits remained even after controlling for baseline bone lesions and the reduction in risk for SREs, suggesting a possible anti-cancer effect of ZOL.

Incorporating data from the Myeloma IX trial, an update to the 2010 Cochrane analysis was presented at ASH 2010. For the outcome of OS, the pooled analysis demonstrated a beneficial effect of ZOL in comparison with CLO (HR 0.83, 95% CI: 0.73–0.94) and ETI (HR 0.48, 95% CI: 0.31–0.71). ZOL was also superior to CLO for PFS (HR 0.88, 95% CI: 0.78–0.99).<sup>45</sup>

Thus far, ZOL is the only bisphosphonate to show a clear OS benefit in MM. Data from the Myeloma IX trial now demonstrate that ZOL has an OS advantage over CLO, even after controlling for baseline bone lesions and the reduction in risk of SREs. In addition, results of the 2010 Cochrane analysis showed no difference in survival outcomes between CLO and PAM. Therefore, the improvement in OS with ZOL shown by the recent Myeloma IX trial suggests ZOL has clinical benefits beyond the prevention of SREs and may be superior to other bisphosphonates in improving survival of patients with MM. Future research should help determine the efficacy of ZOL as a possible anti-cancer treatment in MM.

**Figure 1. Overall survival after treatment with ZOL versus CLO in multiple myeloma<sup>44</sup>**



## Recommendation

Based on the evidence to date, the following is recommended for the addition of bisphosphonates to multiple myeloma therapies for the treatment of multiple myeloma:

- Given the overall survival benefit seen with zoledronic acid in the recent Myeloma IX trial, zoledronic acid is the preferred bisphosphonate for newly diagnosed myeloma patients.

## Hypercalcemia

Approximately 30% of patients with MM develop hypercalcemia, mostly occurring during active disease. Symptoms of acute hypercalcemia may include central nervous system dysfunction (confusion, coma, and obtundation), muscle weakness, pancreatitis, constipation, thirst, polyuria, shortening of the Q-T interval on an electrocardiogram (ECG), and acute renal insufficiency.<sup>11</sup>

Hypercalcemia is typically treated with oral and/or intravenous rehydration. To avoid volume overload and heart failure, adequate urine output should be ensured. In addition, the use of intravenous loop diuretics may be considered to increase urinary calcium excretion once adequate volume repletion has been achieved.<sup>11</sup>

A 2010 Cochrane analysis by Mhaskar, *et al.* pooled data from a total of eight studies (1,934 patients) examining the impact of bisphosphonates on hypercalcemia, compared to placebo/no treatment. Results of the pooled analysis found no overall

reduction in the risk of hypercalcemia with bisphosphonates (RR 0.79, 95% CI: 0.56–1.11;  $p = 0.17$ ).<sup>43</sup> However, the 2010 Cochrane analysis did not include ZOL as one of the bisphosphonates in the analysis.

A pooled analysis of two randomized trials by Major, *et al.* (2001) compared the efficacy and safety of ZOL (4 or 8 mg IV) and PAM (90 mg IV) for treating hypercalcemia of malignancy. Both doses of ZOL were superior to PAM, with normalization of serum calcium levels by day 4 in approximately 50% of patients treated with ZOL and in only 33.3% of patients given PAM.<sup>67</sup> Based on the results of the study by Major, *et al.*, the British Committee for Standards in Haematology/United Kingdom Myeloma Forum (BCSH/UKMF) guidelines (2010) recommend the use of ZOL in patients with moderate-to-severe hypercalcemia.<sup>11</sup>

### Recommendations

Based on the evidence to date, the following is recommended for the use of bisphosphonates in multiple myeloma patients with hypercalcemia:

- All patients with hypercalcemia should be considered for hydration and the use of a loop diuretic.
- All patients with moderate-to-severe hypercalcemia should receive a bisphosphonate.
- Zoledronic acid is the bisphosphonate of choice for the treatment of moderate-to-severe hypercalcemia.

## Choice of Bisphosphonate

Due to the absence of definitive survival data and because results from randomized trials on the incidence of osteonecrosis of the jaw (ONJ) were not available until recently, the Mayo Clinic, International Myeloma Working Group (IMWG), American Society of Clinical Oncology (ASCO), and National Comprehensive Cancer Network (NCCN) guideline committees favoured the use of PAM over ZOL.<sup>9,46–48,50</sup> However, landmark findings from the Myeloma IX trial have demonstrated that ZOL provides a significant survival benefit in newly diagnosed patients with MM.<sup>40</sup> Similar results have been reported in patients with breast cancer.<sup>68</sup> As a

result of this recently released data regarding prolongation of event-free survival (EFS) and OS, the BCSH/UKMF has now recommended that ZOL be the bisphosphonate of choice in patients with MM.<sup>11</sup> Recommendations from existing guidelines on the use of bisphosphonates in multiple myeloma are presented in Table 3.

Despite the strength of efficacy results with ZOL, the choice of a bisphosphonate should always consider patient compliance, choice of administration route, and safety profile, as well as cost and availability.<sup>4</sup>

### Recommendation

Based on the evidence to date, the following is recommended for the choice of bisphosphonate in multiple myeloma:

- Given the recent data from the Myeloma IX trial, zoledronic acid is the bisphosphonate of choice in multiple myeloma; however, patient compliance, choice of administration route, safety profile, cost, and availability are also important considerations.

## Duration of Treatment

A single randomized trial found no benefit of treatment with PAM after tandem stem-cell transplantation. No difference was observed in the proportion of SREs in patients given PAM plus thalidomide (18%) or PAM alone (21%), compared with no

maintenance (24%) after 29 months of follow-up.<sup>35</sup> The majority of more recent guidelines for the use of bisphosphonates therefore recommend a standard duration of no more than two years of treatment in patients with MM.<sup>4,9,47-49</sup> (Table 5)

Guideline	Year	Duration
BCSH/UKMF <sup>11</sup>	2010	<ul style="list-style-type: none"> <li>Given the risk of ONJ, it is reasonable to stop therapy in patients who have achieved a CR or VGPR with transplantation and/or a novel therapy combination and have no active bone disease; this should be at the discretion of the treating hematologist.</li> <li>Therapy should be reinstated at the time of relapse.</li> </ul>
NCCN <sup>46</sup>	2010	NG
EMN <sup>4</sup>	2009	<ul style="list-style-type: none"> <li>BPs should be given for 2 years.</li> <li>After 2 years, continue at physician's discretion.</li> <li>BP therapy should restart upon relapse.</li> <li>Discontinue if patient develops ONJ and only re-initiate if the benefit of treating bone disease surpasses the risk of progressive ONJ.</li> </ul>
BCCA <sup>47</sup>	2008	<ul style="list-style-type: none"> <li>For patients who undergo high-dose chemotherapy and stem-cell transplantation, PAM should be continued at approximately monthly intervals until assessment of response.</li> <li>For patients who do not undergo a stem-cell transplantation, PAM should be continued for 24 months, then stopped; it should only be resumed for another 24 month course if the myeloma again requires systemic treatment.</li> </ul>
ASCO <sup>48</sup>	2007	<ul style="list-style-type: none"> <li>Give BPs monthly for 2 years.</li> </ul>
CCO <sup>49</sup>	2007	<ul style="list-style-type: none"> <li>After 2 years of BP treatment:               <ul style="list-style-type: none"> <li>Patients who have achieved remission and are in a stable plateau phase off treatment should consider discontinuing the use of BPs.</li> <li>Patients who still require active treatment for myeloma should continue BPs, but may consider having the frequency decreased to every 3 months if on PAM or ZOL.</li> <li>Patients whose myeloma becomes active following initial response should resume monthly BP therapy.</li> </ul> </li> </ul>
IMWG Reply to Mayo <sup>50</sup>	2007	<ul style="list-style-type: none"> <li>After 1 year of BP therapy, discontinue if patient has achieved CR or VGPR and has no active bone disease.</li> <li>Continue BP therapy if patient has achieved less than VGPR (&lt;VGPR) and/or has ongoing active bone disease.</li> <li>After 2 years, discontinue BP therapy if patient has no active bone disease.</li> <li>If patient has active bone disease after 2 years of BP therapy, continue at discretion of primary physician.</li> <li>In patients who relapse with new bone disease, reinstitute BP therapy.</li> <li>Discontinue BP therapy if patient presents with ONJ.</li> </ul>
Mayo <sup>9</sup>	2006	<ul style="list-style-type: none"> <li>Give monthly BP therapy for 2 years.               <ul style="list-style-type: none"> <li>After 2 years, discontinue if CR or in stable plateau phase.</li> <li>If disease is active after 2 years, decrease BP frequency to every 3 months.</li> </ul> </li> </ul>
ESMO <sup>51</sup>	2005	<ul style="list-style-type: none"> <li>Long-term BP is recommended.</li> </ul>

ASCO = American Society of Clinical Oncology; BCCA = British Columbia Cancer Agency; BCSH/UKMF = British Committee for Standards in Hematology/United Kingdom Myeloma Forum; CCO = Cancer Care Ontario; EMN = European Myeloma Network; ESMO = European Society for Medical Oncology; IMWG = International Myeloma Working Group; Mayo = Mayo Clinic; NCCN = National Comprehensive Cancer Network

BP = bisphosphonate; CR = complete response; NG = not given; ONJ = osteonecrosis of the jaw; PAM = pamidronate; VGPR = very good partial response; ZOL = zoledronic acid

To date, no clear evidence from clinical trials supports administration of bisphosphonates beyond two years. However, some patients may benefit from prolonged treatment using a reduced dose or dosing schedule.<sup>4</sup> The Myeloma IX trial used bisphosphonate treatment at least until disease progression, with a median duration of 350 days on treatment. Although an early OS benefit was seen with ZOL, the OS curves separated throughout the study, suggesting a continued benefit of ZOL over time.<sup>40,44</sup> The recent BCSH/UKMF guidelines (2010) recommend indefinite use of bisphosphonates until patients achieve a CR or VGPR with transplantation and/or a novel therapy combination, and have no active bone disease.<sup>11</sup>

Most guideline committees agree that after stopping bisphosphonates, it is reasonable to restart these agents in patients who experience disease progression or bone pain.<sup>4,11,47,49</sup> (Table 5) Relapse or progression in bone involvement may be present in patients with active MM who experience increasing bone pain, even in the absence of new SREs. However, to confirm

myeloma bone progression, a full radiographic skeletal survey is required.<sup>4</sup>

To minimize ONJ, an extensive dental evaluation and monitoring protocol should be followed prior to commencing treatment with bisphosphonates. In patients with signs of ONJ during treatment, the European Myeloma Network (EMN) guidelines recommend that bisphosphonates should only be re-initiated if the benefit of treating bone disease surpasses the risk of progressive ONJ.<sup>4</sup> For these patients, a decision should be made at the discretion of the physician, based on the degree of bone destruction.

A full discussion on the management of bisphosphonate-induced ONJ is presented in the paper *A Canadian Perspective on the Management of Bisphosphonate-Related Complications in Multiple Myeloma*. Recommendations from existing guidelines on the optimal duration of bisphosphonates in multiple myeloma are presented in Table 5.

## Recommendations

**Based on the evidence to date, the following is recommended in relation to the duration of bisphosphonate treatment in multiple myeloma:**

- **In the first-line setting, bisphosphonates should be given for up to two years or discontinued earlier if a very good partial response or greater is achieved.**
- **Use of bisphosphonates may be considered in a relapse setting.**
- **Awareness of osteonecrosis of the jaw is recommended before and during bisphosphonate treatment.**

## Adherence

Consideration of factors that influence patient adherence to bisphosphonates is necessary to ensure treatment is effective. CLO is administered orally as a single 1600–2400 mg dose or in two divided doses.<sup>69</sup> Although randomized trials have found long-term compliance with CLO to be reasonable, results of studies in osteoporosis and metastatic bone disease suggest dosing compliance is poor.<sup>4,19,21,70</sup> Poor levels of adherence have also been shown in patients with bone metastases in breast and prostate.<sup>4,71,72</sup> Therefore, despite the convenience of oral bisphosphonates compared with IV preparations, compliance with these agents may be suboptimal and could contribute to a reduction in efficacy.<sup>4</sup>

Greater levels of compliance have been found with IV bisphosphonates.<sup>72</sup> The shorter infusion time (15 minutes) required for ZOL, as compared with other bisphosphonates, allows for administration with less disruption for the patient than the 2–4 hour time required for infusion of PAM.<sup>73,74</sup> The shorter infusion time also means patients spend less time in the outpatient centre, and chairs or stations in the outpatient setting turn over at a faster rate. These time and resource savings may also translate into cost savings of personnel resources and provide a QoL benefit to patients. A study comparing patient preference for either ZOL or PAM showed a 92% preference for ZOL due to the shorter infusion time.<sup>4,75</sup>

## Conclusion

Destruction of bone occurs in the vast majority of patients with multiple myeloma, resulting in significant bone pain, hypercalcemia, and other skeletal-related complications.<sup>4,6</sup> As potent inhibitors of osteoclast-induced bone resorption, bisphosphonates are effective at preventing, reducing, and delaying myeloma-related bone destruction.<sup>4,9</sup> Although bisphosphonates are the standard of care in this setting, no Canadian guidelines are currently in place for their use. The purpose of this document was therefore to present a Canadian perspective on the use of bisphosphonates in multiple myeloma.

Given the methodological difficulties of measuring bone biomarkers, their routine use is not recommended for the assessment of myeloma-related bone destruction at this time. Diagnosis of bone destruction should be performed in all patients using skeletal surveys, with the addition of MRI and CT scans for specific clinical situations. Regardless of whether bone lesions are evident, all patients should be considered candidates for treatment with bisphosphonates.

Results of clinical trials suggest bisphosphonates are effective at preventing, reducing, and delaying skeletal-related complications related to multiple myeloma. In addition, studies comparing zoledronic acid to other bisphosphonates suggest zoledronic acid should be the bisphosphonate of choice for reducing these complications.

Other complications commonly seen in patients with multiple myeloma include bone pain and hypercalcemia.<sup>4</sup> Bone pain should be managed using a multi-modal approach, which

may include the addition of a bisphosphonate, as appropriate. Patients with hypercalcemia should be considered for treatment with rehydration and intravenous loop diuretics. In patients with moderate-to-severe hypercalcemia, zoledronic acid should be given as the bisphosphonate of choice.

To date, zoledronic acid is the only bisphosphonate to show a clear overall survival benefit in multiple myeloma.<sup>4</sup> Data from the Myeloma IX trial now demonstrate that zoledronic acid has an overall survival advantage over clodronate, even after controlling for baseline bone lesions and the reduction in risk of skeletal-related events.<sup>40</sup> In addition, results of the 2010 Cochrane analysis showed no difference in survival outcomes between clodronate and pamidronate.<sup>45</sup> Given the strength of these results, zoledronic acid is currently the bisphosphonate of choice in multiple myeloma. It is important, however, to consider patient compliance, choice of administration route, safety profile, cost, and availability when making any treatment decision.

Some data show that certain anti-myeloma agents, such as thalidomide, bortezomib, and lenalidomide, influence bone metabolism. However, whether these agents also reduce myeloma-related skeletal complications is not clear.<sup>8</sup> Denosumab, a fully human monoclonal antibody targeting RANKL, is being examined in a number of ongoing studies for the prevention of skeletal-related complications, but results are preliminary. Use of these therapies to prevent bone destruction in multiple myeloma is therefore premature and awaits the results of future research.

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