International Myeloma Working Group Recommendations for the Treatment of Multiple Myeloma Related Bone Disease

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ABSTRACT

Purpose: Current treatment options (bisphosphonates, kyphoplasty, vertebroplasty, radiotherapy, and surgery) were evaluated by the IMWG to develop practice recommendations for the prevention and treatment of bone disease associated with multiple myeloma (MM).

Methodology: An interdisciplinary panel of clinical experts on MM and myeloma-related bone disease developed these recommendations based on a review of evidence presented in clinical practice guidelines, clinical studies, and the published literature through June 2012. Expert consensus was used to propose additional recommendations in situations where there were insufficient published data. Levels of evidence and grades of recommendations were assigned and approved by panel members.

Recommendations: Bisphosphonates should be considered in all MM patients receiving frontline anti-myeloma therapy regardless of the presence of osteolytic bone lesions on conventional radiography. However, it is unknown if bisphosphonates offer any advantage in patients with no bone disease assessed by MRI or PET/CT. Intravenous (IV) zoledronic acid (ZOL) or pamidronate (PAM) is recommended for preventing skeletal-related events in MM patients. ZOL is preferred over oral clodronate (CLO) in newly diagnosed MM because of its potential antimyeloma effects and survival benefits. Bisphosphonates should be administered every 3- to 4-weeks IV during initial therapy. ZOL or PAM should be continued in patients with active disease and should be resumed after disease relapse. Bisphosphonates are well tolerated but preventive strategies must be instituted to avoid renal toxicity or osteonecrosis of the jaw. Kyphoplasty should be considered for symptomatic vertebral compression fractures. Low-dose radiation therapy can be used for palliation of uncontrolled pain, impending pathologic fracture, or spinal cord compression. Orthopedic consultation should be sought for long-bone fractures, spinal cord compression, or vertebral column instability.

INTRODUCTION

Multiple myeloma (MM) is an incurable plasma-cell malignancy[1-2], despite the improvement in survival after the introduction of novel agents.[3,4] MM is characterized by osteolytic bone disease due to increased osteoclast activity and reduced osteoblast function.[5-7] Osteolytic lesions are detected in 70-80% of patients at diagnosis and increase the risk for skeletal-related events (SREs; pathologic fractures, spinal cord compression (SCC), the requirement for surgery or palliative radiotherapy to bone)[8,9] that impair survival,[10] undermine quality of life (QoL),[11] and increase treatment costs.[12,13] Previous recommendations for the management of MM with bisphosphonates have been compiled by several organizations (**Table 2**)[15-19], while the IMWG also developed additional recommendations related to bone disease of MM and other plasma cell disorders.[20-22] During the last years, several important studies were reported in the field and thus the IMWG reviewed all clinical evidence and provides, in this paper, recommendations for the prevention and management of bone disease in MM patients.

METHODOLOGY

An interdisciplinary panel of clinical experts on MM and myeloma bone disease developed these recommendations based on a review of evidence published in clinical practice guidelines, randomized clinical studies, meta-analyses, systematic reviews of published clinical studies, observational studies, and case reports through May 2012. Expert consensus was used to propose additional recommendations in situations where there were insufficient published clinical data. Levels of evidence and grades of recommendations were assigned using established criteria (Table 1). The recommendations were initially circulated in draft form to each panel member, who had an opportunity to comment on the levels of evidence as well as the systematic grading of clinical data supporting each recommendation. The manuscript subsequently underwent rounds of revision until consensus was reached by all authors.

GUIDELINE RECOMMENDATIONS

Bisphosphonate Recommendations

Patient Population and Choice of Bisphosphonate

Recommendations:

- Bisphosphonates should be initiated in MM patients, with (grade A) or without (grade B) detectable osteolytic bone lesions in conventional radiography, who are receiving anti-myeloma therapy as well as patients with osteoporosis (grade A) or osteopenia (grade C) due to myeloma. The beneficial effect of ZOL in patients without detectable bone disease by MRI or PET/CT is debatable.
- Intravenous (IV) zoledronic acid (ZOL) and pamidronate (PAM) exhibit comparable efficacy in reducing SREs in patients with MM, and are recommended for preventing SREs in patients with active MM (grade A). Intravenous ZOL is recommended over oral clodronate (CLO) because it is significantly more efficacious at preventing SREs (grade A).
- ZOL rather than CLO is recommended in patients with newly diagnosed MM and bone disease at diagnosis because of its potential anti-myeloma and survival benefit (grade A). ZOL is the only bisphosphonate shown to increase survival in a prospective randomized trial. Clinical outcomes in patients with MM who are not eligible for transplantation may also benefit from combining ZOL with anti-myeloma therapy (grade B).
- Bisphosphonates are recommended for low and intermediate risk aymptomatic MM (AMM) if osteoporosis is identified by DXA scan in doses used in patients with osteoporosis (grade C). For high-risk AMM or if one cannot differentiate between MM-related versus age-related bone loss, the treating physician should consider using dosing and schedule of bisphosphonates as with symptomatic MM, especially in patients with abnormal MRIs (grade D; panel consensus).

- Bisphosphonates are recommended for the treatment of osteoporosis in MGUS in doses used for patients with osteoporosis (grade C). DXA scan should be considered for patients with MGUS because of their reported increase in skeletal-related events compared to age-matched controls (grade B).
- For patients with a solitary lytic lesion and no evidence of osteoporosis, bisphosphonate therapy is not indicated. If osteoporosis is present bisphosphonates should be given as for osteoporosis patients. If multiple lesions are present on MRI the patient has MM bone disease and should be treated with monthly intravenous bisphosphonates (grade C; panel consensus).
- Intravenous ZOL or PAM, or oral CLO can be utilized to control bone pain associated with myeloma bone disease (grade B). PAM 30 mg and 90 mg have shown comparable effects for preventing SREs (grade B).

Evidence:

Patients with Symptomatic Multiple Myeloma: Several studies have evaluated the effects of bisphosphonates (BPs) on SREs and bone pain in patients with MM (**Table 3**). Ibandronate is ineffective in reducing SREs or improving bone pain in patients with MM.[23] The oral BP, CLO, reduced the proportion of patients with MM who experienced progression of osteolytic lesions by 50% compared with placebo (24% vs. 12%; *P*=.026).[24] Use of CLO was also associated with a reduction in the nonvertebral fracture rate (6.8% vs. 13.2% for placebo; *P*=.04) and time to first nonvertebral fracture in patients with newly diagnosed MM.[13] Administration of oral PAM to patients with newly diagnosed MM failed to reduce SREs relative to placebo, and oral PAM is currently not approved for any indication.[25] However, administration of IV PAM to patients with MM with at least one osteolytic lesion resulted in a significant reduction in SREs (24%) versus placebo (41%, *P*<.001). Patients receiving PAM also experienced reduced bone pain and no deterioration in QoL during the 2-year study.[26] A recent study in patients with newly diagnosed

MM (N=504) demonstrated that PAM 30 mg monthly had comparable time to SRE and SRE-free survival time compared to 90mg of PAM. Patients received PAM for at least 3 years, and patients receiving PAM 30 mg showed a trend toward lower risks of osteonecrosis of the jaw (ONJ) and nephrotoxicity relative to PAM 90 mg.[27] However, the study was not powered to show SREs differences between the two dosages of pamidronate but only to show QoL differences.

Zoledronic acid was at least as effective as PAM in reducing the incidence of SREs and pain and delaying the time to first SRE in patients with MM in the conventional chemotherapy era.[28-30] The recent Medical Research Council (MRC) Myeloma IX study demonstrated that a significantly smaller proportion of patients with newly diagnosed MM, receiving ZOL versus oral CLO in addition to first-line anti-myeloma therapy, developed SREs before progression (27.0% vs. 35.3% for CLO; *P*<.001).[31,32] Zoledronic acid reduced the risk of SREs by 26% relative to CLO (HR=0.74, *P*=.0004). Reduction in the risk of any SRE was evident in ZOL-treated patients with (HR=0.774; *P*=.0038) and without (HR=0.53; *P*=.0068) bone lesions at baseline over CLO-treated patients. This is the first time that a bisphosphonate showed a reduction in SREs in myeloma patients who required therapy and had no bone disease, assessed by conventional radiography at baseline. Fewer patients in the ZOL group had vertebral fractures than did those in the CLO group (5% vs. 9%; *P*=.0008), other fractures (5% vs. 7%; *P*=.04) and new osteolytic lesions (5% vs. 10%; *P*<.0001).[32] Furthermore, ZOL significantly reduced the risk of SREs versus CLO regardless of whether patients received thalidomide maintenance or not.[33]

The MRC Myeloma IX study also demonstrated that addition of ZOL to standard first-line anti-myeloma therapy reduced the risk of death by 16% (*P*=.012) and prolonged median overall survival (OS) by 5.5 months (50 vs. 44.5 months) over CLO (N=1,960). Zoledronic acid also reduced the risk of disease progression by 12% (*P*=.018) and increased median progression-free survival (PFS) by 2 months (19.5 vs. 17.5 months) over CLO.[31] In subset analyses, ZOL

significantly reduced the risk of death versus CLO in patients with bone disease at baseline (HR=0.82; *P*=.0107), but not in patients without bone disease at baseline (HR=1.10; *P*=.469).[33] Furthermore, a more recent analysis of MRC-IX data showed that patients not eligible for transplant and who received either CDTa (cyclophosphamide, thalidomide and low dose dexamethasone) or MP (melphalan and prednisone) as anti-myeloma therapy, experienced a higher incidence of CR or VGPR with ZOL versus CLO (CTDa: 33.6% vs. 26.4%, respectively; MP: 6.1% vs. 1.9%, respectively; overall logistic regression *P*=.018).[33] However, it is important to mention that the multiple, unplanned, sub-analyses of the MRC-IX study is a concern for several members of the group.

Other BPs have been also associated with improved survival in subsets of patients. Patients receiving second-line anti-myeloma chemotherapy and treated with PAM experienced a borderline improvement in OS compared to patients treated with placebo (**Table 4**).[34] Similarly, a subgroup of patients without vertebral fractures at presentation experienced a survival advantage with CLO relative to placebo.[35]

Patients with Asymptomatic Myeloma (AMM): Intravenous PAM (60 to 90 mg monthly for 12 months) in patients with AMM reduced bone involvement at progression but did not decrease the risk and the time to progression into symptomatic myeloma.[36] Similarly, intravenous ZOL (4 mg monthly for 12 months) reduced the SRE risk at progression but did not influence the risk of progression of AMM patients.[37]

Several studies have reported the value of MRI (presence of >1 focal lesion and presence of diffuse pattern of marrow infiltration) in detecting patients with AMM at high risk for progression.[38-40] Since there is no clinical trial data on the adjuvant use of bisphosphonates in AMM, it should not be recommended except for a clinical trial of high-risk patients.

Patients with MGUS: MGUS patients are at high risk for developing osteoporosis and pathological fractures.[41] Three doses of ZOL (4 mg intravenously every 6 months) increased

bone mineral density (BMD) by 15% in the lumbar spine and by 6% in the femoral neck in MGUS patients with osteopenia or osteoporosis.[42] Oral alendronate (70 mg/weekly) also increased BMD of the lumbar spine and total femur by 6.1% and 1.5%, respectively, in 50 MGUS patients with vertebral fractures and/or osteoporosis.[43]

Patients with solitary plasmacytoma*:* Patients with solitary plasmacytoma and no evidence of MM do not require therapy with bisphosphonates. However, these patients should have a whole body MRI since in a study of 17 patients diagnosed with a solitary plasmacytoma, all showed additional focal lesions or a diffuse infiltration on MRI, leading to a classification as stage I MM (76%), stage II MM (12%), or stage III MM (12%) using the Durie-Salmon PLUS system.[44]

Route of Administration

Recommendation: Intravenous administration of BPs is preferred choice (grade A). Home IV infusion or oral administration may be considered for patients who cannot receive hospital care (grade D).

Evidence: Strict adherence to dosing recommendations is required for BP therapy to effectively reduce and delay SREs in patients with MM. Each patient prescribed BP therapy should be instructed about the crucial importance of adherence to the dosing regimen. Although a few randomized, placebo-controlled clinical studies suggest that long-term compliance with oral BPs such as CLO is satisfactory in MM patients,[13,24] compliance with oral BP therapy is generally suboptimal.[45] Further, the MRC-IX data strongly support the use of intravenous ZOL over CLO in all outcomes measured, including reduction of SREs and improvement in OS.[31-33] However, oral administration remains an option for patients who cannot receive regular hospital care or in-home nursing visits.

Administration of IV BPs such as ZOL or PAM is generally performed as an outpatient procedure in a clinical environment but may also be performed at home[46], as in breast cancer

patients with bone metastases.[47] Routine patients' monitoring can be combined with the administration of the IV infusion. Infusion times range from 15 minutes for ZOL to 2 to 4 hours for PAM. One study reported that 92% of patients preferred ZOL to PAM because of the shorter infusion time.[48]

Treatment Duration

Recommendations: Intravenous BPs should be administered at 3- to 4-week intervals to all patients with active MM (grade A). ZOL improves OS and reduces SREs over clodronate in patients who received treatment for more than two years; thus it should be given until disease progression and further continued at relapse (grade B). There is not similar evidence for PAM. PAM may be continued in patients with active disease at the physician's discretion (grade D), and PAM therapy should be resumed after disease relapse (grade D).

Because of higher reported rates of ONJ with extended duration of therapy, discontinuation of ZOL or PAM may be considered after 2 years in patients who have achieved a complete remission (grade D; panel consensus).

Evidence: Until data from the Bismarck and other trials using bone resorption markers to dictate dosing frequency, IV bisphosphonates should be administered every 3-4 weeks, as per previous guidelines.[15,19]

The sub-analyses of MRC-IX study showed that among patients who received at least 2 years of bisphosphonate therapy (n = 582), ZOL reduced the incidence of SREs versus CLO (log-rank *P*=.0102). More importantly, in the same group of patients, ZOL improved OS from initial randomization (medians not reached; HR=0.60; *P*=.02) and after first disease progression event versus CLO (34 vs. 27 months, respectively; HR=0.58; *P*=.03).[33] The panel supports the use of ZOL beyond 2 years and until disease progression for patients not in CR, as there are no data for survival or SREs among CR patients. The panel agrees that although administration of

BP therapy beyond 2 years is generally not recommended for patients in CR, some patients may derive benefit from extended therapy. As an alternative to terminating treatment after 2 years, some experts elect to continue BP therapy at a reduced dose or longer intervals.[27,49]

Adverse Events

Recommendations:

- Clinicians should ask their patients about symptoms suggesting adverse events and should monitor their patients for the development of more serious complications. Patients should also be instructed how to recognize AEs and on the importance of early reporting (panel consensus).
- Calcium and vitamin D3 supplementation should be used to maintain calcium homeostasis (grade A). Calcium supplementation should be used with caution in patients with renal insufficiency. All BP-treated patients should have creatinine clearance (CrCl), serum electrolytes, and urinary albumin monitored (grade A).
- Preventive strategies should be adopted to avoid ONJ. Patients should receive a comprehensive dental examination and be educated regarding optimal dental hygiene (grade C; panel consensus). Existing dental conditions should be treated before initiating BP therapy (grade C; panel consensus).
- After BP treatment initiation, unnecessary invasive dental procedures should be avoided and dental health status should be monitored on at least an annual basis (grade C). Patients' ongoing dental health status should be monitored by a physician and a dentist (grade D; panel consensus). Dental problems should be managed conservatively if possible (grade C). Temporary suspension of BP treatment should be considered if invasive dental procedures are necessary (grade D). The panel consensus is to stop bisphosphonates for 90 days before and after invasive dental procedures (tooth extraction, dental implants and

surgery to the jaw). Bisphosphonates do not need to be discontinued for routine dental procedures including root canal.

- Initial treatment of ONJ should include discontinuation of BPs until healing occurs (grade C). The decision to restart BPs should be individualized, until the results of prospective long-term studies are available (grade D). The physician should consider the advantages and disadvantages of continued treatment with BPs, especially in the relapsed/refractory MM setting (grade D).

Evidence: Bisphosphonate therapy is generally well tolerated in patients with MM. Potential adverse events (AEs) associated with BP administration include hypocalcemia and hypophosphatemia, gastrointestinal events after oral administration, inflammatory reactions at the injection site, and acute-phase reactions after IV administration of aminobisphosphonates. Renal impairment and ONJ represent infrequent but potentially serious AEs with BP use.

Patients receiving anti-resorptive therapy may develop hypocalcemia and hypophosphatemia. Hypocalcemia is usually relatively mild and asymptomatic with BP use in most MM patients, and the incidence of symptomatic hypocalcemia is much lower in MM patients compared to patients with solid tumors. Although severe hypocalcemia has been observed in some patients,[50] these events are usually preventable via the administration of oral calcium and vitamin D3. Patients should routinely receive calcium (600 mg/day) and vitamin D3 (400 IU/day) supplementation since 60% of MM patients are vitamin D deficient or insufficient.[51,52] Since vitamin D deficiency increases bone remodeling, in particular PTH levels, it is very important that patients be calcium and vitamin D sufficient.[53] Calcium supplementation should be used with caution in patients with renal insufficiency.

Bisphosphonate infusions are associated with both dose- and infusion rate-dependent effects on renal function. The potential for renal damage is generally dependent on the concentration of BP in the bloodstream, and the highest risk is observed after administration of high dosages or

rapid infusion. Both ZOL and PAM have been associated with acute renal damage or increases in serum creatinine.[26,29-31,33,54-57] Patients should be closely monitored for compromised renal function by measuring CrCl before administration of each IV BP infusion. Patients with mild to moderate renal impairment, defined by a CrCl rate of 30-60 mL/min, should receive reduced doses of CLO and ZOL under close clinical monitoring, as previously recommended.[19] No change to ZOL infusion time is recommended. PAM should be administered via extended infusion duration (>4 hours) and clinicians should also consider reducing the initial dose in patients with renal impairment. PAM and ZOL are not recommended for patients with CrCl <30 mL/min.

Early diagnosis is crucial, and urinary albumin and serum electrolytes in addition to CrCl rates should be monitored in these patients. Oral CLO is contraindicated if CrCl is <12 mL/min. Adherence to recommended infusion protocols regarding dosage, infusion time, serum creatinine levels, and hydration is mandatory to minimize the potential for renal damage. Bisphosphonate therapy should be discontinued in patients experiencing renal problems until serum creatinine levels return to within 10% of baseline values.

ONJ, characterized by exposed bone in the mouth that does not heal with 6-8 weeks of therapy, is a potentially serious complication of BP therapy. Retrospective studies have suggested that 4% and 11% of patients develop ONJ.[58,59] Zoledronic acid has been associated with a higher reported rate of ONJ than other BPs, and the cumulative dose and duration of therapy are believed to contribute to the development of ONJ.[58,59] In the MRC-IX study, the ONJ incidence with ZOL was approximately 1% per year (5% at a median follow-up of 4.8 years); these patients did not receive mandatory dental prophylaxis as part of this trial.[31,33] Among patients who received ZOL beyond 2 years, 4.1% developed ONJ.[33] In another prospective study comparing ZOL with denosumab in patients with solid tumors and bone metastases or with MM (10% of the population studied) the incidence of ONJ after 2 years was 1.3% with ZOL and

1.1% with denosumab.[56] Additional risk factors for ONJ include dental procedures, local infections, and treatment with corticosteroidss.[58-60] Three studies of patients with MM or solid tumors demonstrated that implementation of appropriate preventive measures greatly reduced the number of ONJ cases.[61-63] Clinical studies support restarting BP therapy after healing of ONJ. A long-term follow-up study of 97 MM patients with ONJ demonstrated that patients who developed ONJ after dental procedures were less likely to have recurrence or non-healing lesions after BP re-initiation following ONJ healing compared to patients who developed spontaneous ONJ.[60] Recurrence of ONJ was linked to rechallenge with BP therapy, mainly in the relapsed setting. [60]

Kyphoplasty and Vertebroplasty

Recommendation: Balloon kyphoplasty should be considered for symptomatic vertebral compression fractures (VCFs) and is the procedure of choice to improve QoL in patients with painful VCFs (grade A). The role of vertebroplasty for myeloma patients is less clear as there is no randomized trial of vertebroplasty in myeloma patients.

Evidence: Several studies have demonstrated that balloon kyphoplasty (BKP) or vertebroplasty are well-tolerated and effective procedures that provide pain relief and improve functional outcomes in patients with painful neoplastic spinal fractures. A single randomized study of 134 patients with bone metastases due to solid tumors and MM demonstrated that treatment of VCFs with BKP was associated with clinically meaningful improvements in physical functioning, back pain, QOL, and ability to perform daily activities relative to nonsurgical management. These benefits persisted throughout the 12-month study.[64] A meta-analysis of 7 nonrandomized studies of patients with MM or osteolytic metastasis revealed that BKP was associated with reduced pain and improved functional outcomes, benefits that were maintained up to 2-years post-procedure (N = 306). BKP also improved early vertebral height loss and spinal deformity,

but these effects were not long-term **(Table 5**).[65] Similarly, a retrospective review of 67 patients with MM-related VCFs demonstrated that vertebroplasty provided clinically meaningful improvements in physical functioning, pain, and mobilit throughout 12 months of follow-up.[66] Several small non-randomized studies of BKP or BKP and vertebroplasty generated comparable results.[67-69] However, the role of vertebroplasty for myeloma patients remains debatable in the absence of prospective data[70], as two randomized trials failed to show any benefit of vertebroplasty in patients with osteoporotic fractures versus conservative therapy.[71,72] Furthermore, a meta-analysis of 59 studies (56 case series) showed that BKP appears to be more effective than vertebroplasty in relieving pain secondary to cancer-related VCFs and is associated with lower rates of cement leakage.[73]

Radiation Therapy

Recommendation: Low-dose radiation therapy (up to 30 Gy) can be used as palliative treatment for uncontrolled pain, for impending pathologic fracture, or impending SCC. Upfront external beam radiation therapy should be considered for patients with plasmacytoma, extramedullary masses, and SCC (grade C). However, the use of radiotherapy for local disease control and palliation should be used judiciously and sparingly depending on patient's presentation, need for urgent response, and prior treatment history and response. It should be limited as much as possible to spare the patient's marrow function. Current novel agents work rapidly and should decrease the need for palliative radiotherapy.

Evidence: Several studies, the majority of which were retrospective and included relatively small patient cohorts, demonstrated that radiotherapy provided pain relief, decreased analgesic use, promoted recalcification, reduced neurologic symptoms, and improved motor function and QoL in patients with MM.[74-76] In addition, the total administered dose should be limited and the field of therapy restricted, especially when the aim of treatment is pain relief rather than

treatment or prevention of pathologic fractures. A single 8- to 10-Gy fraction is generally recommended. Indeed, single fractions are increasingly preferred to fractionated treatment. No difference in rapidity of onset or duration of pain relief was observed between a single 8-Gy fraction and a fractionated 2-week course of 30 Gy in a randomized study of 288 patients with widespread bony metastases, including 23 patients with MM.[77]

MM accounts for 11% of the most prevalent cancer diagnoses causing SCC.[78] In the largest retrospective series to-date, radiotherapy alone improved motor function in 75% of patients with MM and SCC. One-year local control was 100% and one-year survival was 94%.[79]

Surgery

Recommendation:

- Orthopedic consultation should be sought for impending or actual long-bone fractures, bony compression of the spinal cord, or vertebral column instability (grade D).
- Consideration and indications for surgery should be done in consultation with the treating oncologist/hematologist and the orthopedic and neurosurgeon to determine when MM treatment can be safely restarted.

Evidence: Surgery is usually directed toward preventing or repair of axial fractures, unstable spinal fractures and SCC in myeloma patients. Decompression laminectomy is rarely required in MM patients, but radioresistant MM or retropulsed bone fragments may require surgical intervention.[80] In a relatively large study, 75 MM patients were treated surgically (83 interventions) for skeletal complications of the disease. Most of the lesions were in the axial skeleton or the proximal extremities apart from one distal lesion of the fibula, and most surgery was performed in the spine (35 patients). Surgical treatment in these patients was mostly limited to a palliative approach and was well tolerated.[81]

CONCLUSION

Bisphosphonates are recommended in all MM patients requiring frontline therapy, regardless of the presence of bone disease at diagnosis, assessed by conventional radiography. Although ZOL, PAM, and CLO reduce SREs and control bone pain compared to placebo, ZOL is associated with improved survival of patients with newly diagnosed MM and bone disease and reduces SREs over CLO. This benefit remains in patients who receive ZOL or CLO for more than two years. Therefore, ZOL should be given until disease progression with the possible exception of patients who have achieved CR, for whom there are no data regarding the survival advantage of ZOL. For PAM there are no data demonstrating a survival advantage and can be given up to 2 years and continued at the physician discretion in patients with active myeloma. Bisphosphonate therapy is generally well tolerated, but preventive strategies should be adopted to avoid renal impairment or ONJ. Local radiotherapy should be considered for painful bone lesions, and kyphoplasty may be used for the treatment of VCFs (**Table 6**).

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TABLES

Table 1. Levels of Evidence and Grades of Recommendations

Type of Evidence	
Level	
I	Evidence obtained from meta-analysis of multiple well designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power)
II	Evidence obtained from at least one well designed experimental study. Randomized trials with high false-positive and/or -negative errors (low power)
III	Evidence obtained from well designed, quasi-experimental studies such as non-randomized, controlled single-group, pre-post, cohort, time, or matched case-control series
IV	Evidence from well designed, non-experimental studies such as comparative and correlational descriptive and case studies
V	Evidence from case reports and clinical examples
Grade of Recommendation	
Grade	
A	There is evidence of type I or consistent findings from multiple studies of types II, III, or IV
B	There is evidence of types II, III, or IV and findings are generally consistent
C	There is evidence of types II, III, or IV but findings are inconsistent
D	There is little or no systematic empirical evidence

Table 2. Summary of Bisphosphonate Guidelines in Multiple Myeloma

	NCCN[14]	ESMO[17]	ASCO[15]	MAYO[16]	IMWG Reply to MAYO[18]	EMN[19]
Patient population	Active or all other stages of myeloma Adjunctive therapy for bone disease	Stage III or relapsed disease receiving conventional-dose chemotherapy	Lytic disease (lytic destruction of bone or compression fracture of the spine from osteopenia) on plain radiographs or imaging studies Patients with osteopenia but no evidence of lytic bone disease based on normal plain radiograph or BMD measurements	All pts with lytic bone disease on plain radiographs; pts with osteopenia or osteoporosis on BMD studies	In addition to radiographs, other imaging studies (MRI, CT, CT/PET)	All patients with lytic bone disease on plain radiographs; patients with osteopenia or osteoporosis on BMD studies; patients on chemotherapy
Administration	IV	Oral or IV	Oral or IV	IV	IV or oral	IV or PO
PAM IV infusion time	N/A	N/A	At least 2 hours	At least 2 hours	N/A	2 to 4 hours
Duration/frequency	N/A	Long-term	Monthly for 2 yr	Monthly for 2 yr After 2 yr: Discontinue if CR or stable plateau phase; ↓ to every 3 mo if active disease	2 yr After 1 yr: Discontinue if CR or VGPR and no active bone disease Continue if <VGPR and/or ongoing active bone disease After 2 yr: Discontinue if no active bone disease If active bone disease, continue	2 yr . After 1 yr: Continue at physician's discretion Restart on relapse

at own discretion

Monitoring	Chronic users should be monitored for renal function and ONJ Smoldering/stage I MM—use BP in a trial with yearly bone surveys	N/A	Monitor serum creatinine before each PAM or ZOL dose Regularly monitor serum calcium, electrolytes, phosphate, magnesium, hematocrit/ hemoglobin	N/A	N/A	Monitor patients for compromised renal function (creatinine clearance) Patients with compromised renal function should have creatinine clearance rates, serum electrolytes, and albuminuria monitored
Choice	PAM or ZOL	N/A	ZOL, PAM, or CLO (non-US)	PAM (favorable) or ZOL	PAM, ZOL, or CLO	ZOL, PAM, or CLO (where indicated)

BMD, bone mineral density; VGPR, very good partial response; CR, complete response; MM, multiple myeloma; NCCN, National Comprehensive Cancer Network; ESMO, European Society for Medical Oncology; IMWG, International Myeloma Working Group; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; ONJ, osteonecrosis of the jaw; BP, bisphosphonate; PAM, pamidronate; ZOL, zoledronic acid; CLO, clodronate.

Adapted with permission from Terpos et al.[19]

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Table 3. Large, Controlled Studies of Bisphosphonate Therapy in Multiple Myeloma

Authors (year)	BP	Dosage	MM, N[a]	Reduction of SREs[b]	Survival Benefit
Placebo-Controlled Trials					
Lahtinen et al, 1992[24] Laakso et al, 1994[82]	CLO	2.4 g/day, PO, for 2 yr	350	Yes	NE
McCloskey et al 1998[13] and 2001[35]	CLO	1.6 g/day, PO	530	Yes	Subset[c]
Brincker et al 1998[25]	PAM	300 mg/day, PO	300	No	No
Berenson et al 1996[26] and 1998[34]	PAM	90 mg, IV, q4wk; 21 cyc	392	Yes	Subset[d]
Menssen et al 2002[23]	IBN	2 mg, IV q mo	198	No	No
PAM (90 mg)—Controlled Trials					
Gimsing et al 2010[27]	PAM	30 mg vs 90 mg IV q4wk	504	Comparable	No change
Berenson et al 2001[28]	ZOL	2 or 4 mg, IV q mo	108	Yes	NE
Rosen et al 2001[29] and 2003[30]	ZOL	4 or 8 mg, IV q mo	513	Yes	Subset[e]
CLO (1.6 g)—Controlled Trial					
Morgan et al 2010[31], 2011[32], 2012[33]	ZOL	4 mg, IV q3-4wk	1,960	Yes	Yes

[a]Number of patients with MM.
[b]SREs include new lytic lesions, vertebral and nonvertebral fractures, and need for radiation or surgery to bone.
[c]In post-hoc analysis, patients without vertebral fracture at study entry survived significantly longer on CLO (median survival 23 months) compared with placebo.
[d]Survival in patients with more-advanced disease was significantly increased in the PAM group (median survival 21 vs 14 months; P = .041 adjusted for baseline serum β_2-microglobulin and Eastern Cooperative Oncology Group performance status).
[e]Survival benefit with ZOL over PAM in a subgroup of patients who had elevated baseline bone-specific alkaline phosphatase levels.
Adapted from Terpos E, et al. *Ann Oncol*. 2009;20(8):1303-1317. Additional data: Gimsing et al. *Lancet Oncol* 2010;11(10):973-982; Morgan et al. *Lancet* 2010;376(9757):1989-1999.

Table 4. Clinical Outcomes in Patients With Multiple Myeloma Treated With Bisphosphonate Therapy

Study/Reference	Patient Population	Treatment	Overall Survival			Progression-Free Survival		
			Median, mo	HR (95% CI)	*P* value	Median, mo	HR (95% CI)	*P* value
MRC Myeloma IX (Morgan et al 2010)[31]	Newly diagnosed patients with MM	ZOL (n = 981)	50	.842 (0.74-0.96)	.012	19.5	.883 (0.80-0.98)	.018
		CLO (n = 979)	44.5			17.5		
Berenson et al 1998[34]	Patients with MM who received 2nd-line antimyeloma chemotherapy (stratum 2)	PAM (n = 66)	21	N/A	.081	N/A	N/A	N/A
		PLA (n = 65)	14					
McCloskey et al 2001[35]	Patients with no vertebral fractures at presentation	CLO (n = 73)	59	.62 (.43 - .87)	.004	N/A	N/A	N/A
		PLA (n = 80)	37					

Abbreviations: CI, confidence interval; CLO, clodronate; HR, hazard ratio; MM, multiple myeloma; PAM, pamidronate; PLA, placebo; ZOL, zoledronic acid.

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Table 5. Efficacy of Balloon Kyphoplasty for Malignant Spinal Fractures: Results of a Meta-Analysis

Variable	Studies, N	Patients/Levels, N	Size of Effect (95% CI); *P* value; I^2
Pain: VAS score (0 - 10)			
Basal - postoperative	4[83-86]	172 patients	SMD: 3.85 (2.99, 4.71); *P* < .001; 79%
Baseline - end of follow-up	3[84-86]	109 patients	SMD: 4.27 (2.38, 6.21); *P* < .001; 93%
Functional capacity:			
ODI (0 - 100)			
Baseline - postoperative	4[83,85-87]	173 patients	WMD: –28.78 (–11.5, – 46.0); *P* = .001; 99%
Baseline - <6 months	2[83,87]	82 patients	WMD: –16.39 (–14.25, –18.5); *P* = .001; 0%
Baseline - 2 years	2[85,86]	91 patients	WMD: –41.95 (–39.42, –44.5); *P* = .001; 0%
Kyphotic deformity (Cobb angle):			
Basal - postoperative	3[85,86,88]	180 levels	SMD: –0.69 (–0.20, –1.16); *P* = .001; 78%
Baseline - end of follow-up	3[85,86,88]	155 levels	SMD: –0.39 (0.05, –0.84); *P* = .08; 74%
Vertebral height:	3[83,84,88]	342 levels	RR:47% (33%, 61%); 38%
Percentage of restitution	2[85,86]	158 levels	
Increase (mm):			
Anterior vertebral body			
Basal - postoperative			SMD:0.28 (0.06, 0.51); *P* = .01; 0%
Baseline - end of follow-up			SMD: 0.15 (–0.16, 0.45); *P* = .35; 37%
Midline vertebral body			
Basal - postoperative			SMD:0.28 (0.003, 0.56); *P* = .04; 34%
Baseline - end of follow-up			SMD:0.15 (–0.17, 0.46); *P* = .35; 41%

All based on a random effects meta-analysis.
VAS, Visual Analogue Scale. SMD, standardized mean difference ODI, Oswestry Disability Index. WMD, weighted mean difference. RR, rate ratio. CI, confidence interval.
Reproduced with permission from Bouza et al.[82]

Table 6. New Recommendations for the Use of Bisphosphonates in Multiple Myeloma

Patient population	Newly diagnosed patients with MM who are requiring anti-myeloma treatment (regardless of bone status)
Administration	IV
Duration/frequency	Monthly during initial therapy and ongoing in patients who are not in remission After 2 years, discontinue if CR and no active bone disease. Continue if ≤VGPR and/or ongoing active bone disease
Monitoring	Monthly creatinine clearance
Choice	ZOL (first option) PAM (second option) CLO (only in patients who cannot come to hospital-severe disabilities)

Abbreviations: CR, complete response; IV, intravenous; MM, multiple myeloma; PAM, pamidronate; VGPR, very good partial response; ZOL, zoledronic acid.