Bisphosphonate Guidelines for treatment and prevention of myeloma bone disease

Oi Lin Lee[1], Noemi Horvath[1,2], Cindy Lee[2,3], Doug Joshua[2,4,5], Joy Ho[2,4,5], Jeff Szer[2,6,7], Hang Quach[2,6,8], Andrew Spencer[2,6,9], Simon Harrison[2,6,10], Peter Mollee[2,11,12], Andrew W. Roberts[2,6,7,13], Dipti Talaulikar[2,14,15], Ross Brown[2,4], Bradley Augustson[2,16], Silvia Ling[2,17,18], Wilfrid Jaksic[2,3] John Gibson[2,4,5], Anna Kalff[2,9], Anna Johnston[2,19,20], Akash Kalro[2,21], Chris Ward[2,5,22], H. Miles Prince[2,10,6] and Andrew Zannettino[2,23,24]

[1]Department of Haematology, Royal Adelaide Hospital, Adelaide, Australia

[2]Medical and Scientific Advisory Group, Myeloma Australia, Richmond, Australia

[3]Department of Haematology, Queen Elizabeth Hospital, Adelaide, Australia

[4]Department of Haematology, Royal Prince Alfred Hospital, Camperdown, Australia

[5]Sydney Medical School, University of Sydney, Australia

[6]Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Parkville, Australia

[7]Department of Clinical Haematology and BMT, Royal Melbourne Hospital, Parkville, Australia

[8]Department of Haematology, St Vincent's Hospital, Melbourne, Australia

[9]Department of Haematology, The Alfred Hospital, Melbourne, Victoria

[10]Department of Haematology, Peter MacCallum Cancer Centre, Melbourne, Australia

[11]Department of Haematology, Princess Alexandra Hospital, Brisbane, Australia

[12]School of Medicine, University of Queensland, Brisbane, Australia

[13]Walter and Eliza Hall Institute of Medical Research, Parkville, Australia

[14]Department of Haematology, Canberra Hospital, Canberra, Australia

[15]Australian National University, Canberra, Australia

[16]Department of Haematology, Sir Charles Gairdner Hospital, Perth, Australia

[17]Liverpool Hospital, Liverpool, New South Wales, Sydney, Australia

[18]South Western Sydney Clinical School, University of New South Wales, Sydney, Australia

[19]Department of Haematology, Royal Hobart Hospital, Hobart, Australia

[20]Faculty of Health, University of Tasmania, Hobart, Australia

[21]Department of Haematology, Royal Darwin Hospital, Darwin, Australia

[22]Department of Medicine, Royal North Shore Hospital, St Leonards, Australia

[23]Adelaide Medical School, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, Australia

[24]Cancer Theme, South Australian Health and Medical Research Institute

Corresponding author:

Professor Andrew C. W. Zannettino

Adelaide Medical School

Faculty of Health and Medical Sciences

University of Adelaide, South Australia, AUSTRALIA, 5000

Telephone: (61) (8) 8128 4390

Email: andrew.zannettino@adelaide.edu.au

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Abstract

Multiple myeloma (MM) is a haematological malignancy characterised by the clonal proliferation of plasma cells (PC) in the bone marrow (BM). More than 80% of patients with MM display evidence of myeloma bone disease (MBD), characterized by the formation of osteolytic lesions throughout the axial and appendicular skeleton. MBD significantly increases the risk of skeletal-related events (SREs) such as pathologic fracture, spinal cord compression and hypercalcaemia. MBD is the result of MM PC-mediated activation of osteoclast activity and suppression of osteoblast activity. Bisphosphonates (BPs), pyrophosphate analogues with high bone affinity, are the only pharmacological agents currently recommended for the treatment and prevention of MBD and remain the standard of care. Pamidronate and zoledronic acid are the most commonly used BPs to treat MBD. Although generally safe, frequent high doses of BPs are associated with adverse events such as renal toxicity and osteonecrosis of the jaw (ONJ). As such, optimal duration and dosing of BP therapy is required in order to minimize BP-associated adverse events. The following guidelines provide currently available evidence for the adoption of a tailored approach when using BPs for the management of MBD.

Introduction

MM is a clonal plasma cell malignancy characterized by osteolytic bone disease leading to devastating complications including debilitating pain, pathological fractures and spinal cord compression resulting in significant disability. MBD is observed in more than 80% of patients during the course of their disease and severely affects their quality of life, increases morbidity and has a significant economic impact (1, 2). Moreover, MBD is also associated with a 30% increased risk of mortality (3).

Table 1 National Health and Medical Research Council grades for recommendation and levels of evidence(4, 5)

Grades of recommendation	Levels of evidence
A Body of evidence can be trusted to guide practice	I Evidence obtained from a systematic review of all relevant randomized controlled trials
B Body of evidence can be trusted to guide practice in most situations	II Evidence obtained from at least one properly designed randomized controlled trial
C Body of evidence provides some support for recommendation(s) but care should be taken in its application	III-1 Evidence obtained from well-designed pseudo-randomized controlled trials III-2 Evidence obtained from comparative studies with concurrent controls and allocation not randomized, cohort studies, case-control studies, or interrupted time series with a control group III-3 Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
D Body of evidence is weak and recommendation must be applied with caution	IV Evidence obtained from case series, either post-test or pretest/post-test

Pathophysiology of MBD

Bone health, under normal physiological conditions, is maintained by a dynamic balance between bone formation by osteoblasts and bone resorption by osteoclasts and occurs in response to physiological influences and mechanical forces. In MM, this tightly controlled process of bone formation and resorption is disrupted leading to increased osteoclast activity and decreased osteoblast activity (6, 7). A number of soluble MM PC-derived factors have been implicated in promoting bone destruction. Furthermore, factors released by bone resorption further promote MM cell growth perpetuating the vicious cycle of malignant cell expansion and bone destruction. Factors that influence osteoclast activation include the receptor activator of NF-κB ligand (RANKL)/osteoprotegerin (OPG) ratio (6, 8-10), macrophage inhibitory protein-1α (MIP-1α) (11, 12), IL-6 (13) and tumour necrosis factor-α (TNFα) (14). The factors that inhibit osteoblast activity include the inhibitors of the Wnt signalling pathway such as Dickkopf-1 (Dkk-1), soluble-frizzled receptor-like proteins (sFRPs) and sclerostin (15-18).

Definition and diagnosis of MBD

MBD is traditionally diagnosed by plain radiograph-based skeletal surveys, which reveal the presence of osteolytic bone lesions or osteoporosis with compression fractures that are attributed to the underlying clonal PC disorder (19, 20). However, a destructive bone lesion needs to be at least 1 cm and associated with a loss of at least 50% of the bone mineral content before it can be detected by plain radiograph (21). Whole body low dose CT (WBLD-CT), PET/CT and whole body MRI WB-MRI) represent more sensitive imaging modalities for the detection of osteolytic lesions. However, if WB-MRI is not widely available, MRI of the spine and pelvis will detect approximately 90% of all osteolytic lesions. (22).

Most existing guidelines still recommend skeletal survey by conventional radiography as the initial method for the detection of MBD. Other modalities such as WBLD-CT, MRI or PET/CT are indicated

when there is a suspicion of bony disease even if conventional radiography is negative (20, 23-25). A systematic review comparing conventional imaging with more modern techniques supports the use of WBLD-CT or MRI (26). With the availability and use of more sensitive modalities, the 2014 IMWG guidelines recommends that osteoporosis or compression fracture alone without the presence of osteolytic lesion is insufficient to meet the criteria. Notably, bone densitometry or evidence of increased FDG uptake on PET without accompanying destructive bone lesions are also insufficient to meet the diagnostic criteria of MBD (20). Recently, the IMWG recommended that patients with high-risk smouldering MM should be treated as symptomatic MM based on certain biomarkers of malignancy, including more than 1 focal lesion of at least 5 mm on MRI (20). Focal lesions on MRI indicate bone marrow involvement and not actual bone destruction (22).

Recommendations

- **Skeletal survey by conventional radiology may be performed initially but WBLD-CT or PET/CT should be used to clarify ambiguous radiological findings or if suspicion of bony disease is high even with negative conventional radiological findings. (Grade A, Level I)**
- **MBD is defined as 1 or more osteolytic lesions seen on conventional radiology, CT (including WBLD-CT) or CT/PET. On CT, lesions have to be ≥5 mm. Increased activity on PET scan without the accompanying destructive bone lesion is not sufficient. (Grade A, Level I)**
- **In patients with smouldering MM, more than 1 focal lesion on MRI at least 5 mm is also an indication for treatment. (Grade A, Level I)**
- **Osteoporosis or compression fracture alone without accompanying osteolytic bone lesion is also insufficient to meet the criteria. Neither are bone densitometry studies. (Grade A, Level II)**
- **Bone (technecium-99) scintigraphy has no role in the diagnosis of MBD. (Grade A, Level 1)**

Bisphosphonates (BPs)

1. Mechanism of action

BPs are pyrophosphate analogues which bind avidly to hydroxyapatite and are incorporated into areas of active bone remodelling (29). All BPs share the same core Phosphate-Carbon-Phosphate backbone but their affinity for hydoxyapatite and their potency depends on the composition of the 2 side chains coupled to the central carbon atom of the nucleus (30). The presence of a nitrogen or amino group, as in pamidronate and zoledronic acid renders them 100 to 10 000 fold more potent than the non-nitrogen containing etidronate and clodronate (31). BPs are taken up by osteoclasts during bone resorption and this result in reduced osteoclast recruitment, maturation and activity and induction of apoptosis (32, 33). In addition, recent studies suggest that BP can also stimulate osteoblastic bone formation *in vitro* and *in vivo* (34-36). To date, BPs are the only pharmacological agents currently recommended for the treatment and prevention of MBD. While agents such as the anti-RANKL antibody Denosumab are used in patients with bone metastasis in breast and prostate cancer, Denosumab is still undergoing clinical trials in MM patients **(27, 28)**.

2. Evidence for using BP in MM

Oral clodronate has been shown to reduce the incidence of SRE in patients compared to a placebo-control group (37, 38). In patients with advanced disease and evidence of at least 1 osteolytic lesion, pamidronate was shown to significantly reduce SRE compared to placebo. Pamidronate-treated patients also experienced reduced bone pain (39, 40). Zoledronic acid is at least as effective as pamidronate in reducing SRE, pain and delaying time to SRE in MM patients (41-43).

3. Comparison between BPs

Currently, the two most commonly used BPs in MBD are pamidronate and zoledronic acid. Zoledronic acid is the most potent BP and has demonstrated up to 180-fold potency compared to pamidronate (27). A randomized, double-blind study comparing pamidronate and zoledronic acid in

MM patients with lytic bone lesions and breast cancer patients with skeletal metastasis did not show any difference in terms of SRE in the MM cohort (43). Although a more recent observational study suggested superiority of zoledronic acid over pamidronate in terms of both reduction of SRE and overall survival (OS), no long term results from randomized controlled trials directly comparing these BPs have been reported (44).

The Medical Research Council (MRC) of UK compared zoledronic acid with oral clodronate in symptomatic newly diagnosed MM patients. Not only did patients treated with zoledronic acid experience less SRE, they also showed increased OS and progression free survival (PFS) additional to that attributed to the effects of prevention of SRE (45). Other BPs have also been associated with improved survival; relapsed myeloma patients receiving pamidronate with second line therapy have slightly improved OS compared with the placebo-treated group (40). These results support preclinical studies of anti-myeloma effects of BPs (46-48). Furthermore, a Cochrane meta-analysis of 20 trials concluded that zoledronic acid improves OS when compared to placebo or etidronate but not compared to the other BPs (49).

4. Adverse effects

Adverse effects of BPs include inflammatory reactions at the site of injection, acute phase reactions like transient fever, myalgia and flu-like symptoms, hypocalcaemia, hypophosphataemia, renal impairment and osteonecrosis of the jaw (ONJ) (50-53). Rarely, subtrochanteric and diaphyseal femoral fractures have also been reported (54). Ocular side effects including conjunctivitis, uveitis, episcleritis, scleritis and keratitis have also been associated with BP use. Symptoms become apparent within a few hours to days after commencement, requiring discontinuation (55-58). Acute phase reactions often occur after the first infusion and symptomatic treatment is normally sufficient (59). Oral BPs may also be associated with gastrointestinal side effects like nausea, diarrhoea and abdominal pain (38).

4.1. Renal impairment

Intravenous BPs are not metabolized but are eliminated exclusively by the kidneys (29, 30). While acute and chronic renal impairment can occur, renal damage is dependent on drug levels in the blood. The risk is highest with high dosage and rapid infusion rates (43). Renal injury may be multifactorial and may be due to glomerular, tubular or interstitial injury (60, 61). Pamidronate is associated with acute kidney injury and nephrotic range proteinuria; this is attributed to a number of different mechanisms including collapsing focal segmental glomerulosclerosis (62, 63). In contrast, zoledronic acid is more often associated with tubular toxicity resulting in acute tubular necrosis (64).

True incidence of BP-induced renal impairment is unknown, however an elevated baseline creatinine is a risk factor (65). A study comparing zoledronic acid and pamidronate in patients with skeletal lesions in breast cancer and MM found that the incidence of renal deterioration was similar in both drugs (10.7% in zoledronic acid vs 9.3% in pamidronate) (43). Notably, acute kidney injury from either drug may progress to renal failure requiring dialysis (60).

Renal impairment has also been rarely associated with oral clodronate especially when used simultaneously with non-steroidal anti-inflammatory drugs and as such, the manufacturers do not recommend its use in patients with severe renal impairment (66).

4.2. ONJ

While occurring in only a minority of patients, ONJ is a potentially serious adverse effect of BPs. ONJ commonly occurs following dental procedures and is characterized by exposed bone in the oral cavity with subsequent necrosis and bone death (67).

4.2.1. Pathogenesis of ONJ

The aetiology of ONJ remains unclear but may be due to a combination of infection, suppression of bone turnover and reduced vascularity of the bones of the maxilla and mandible. Dental infection is a well-established risk factor as infections are known to stimulate bone resorption (68). Moreover, bacteria and neutrophils are often seen in affected tissue (69-71).

Suppression of bone remodelling by BPs may play an important role in the pathogenesis of ONJ. This is supported by increased risks with higher potency BPs like zoledronic acid in comparison with pamidronate and alendronic acid (69, 72, 73). ONJ has also been described with other anti-resorption drugs like the anti-RANKL antibody, denosumab (74). The predisposition of the jaw to osteonecrosis has been attributed to the increased rate of remodelling in the jaw due to biomedical load resulting in microtrauma and heightened bone turnover (75).

Furthermore, osteonecrosis is classically associated with an interruption of the blood supply (76) and BPs are known to have anti-angiogenic properties (77, 78). ONJ has also been described in cancer patients treated with other anti-angiogenic agents such as bevacizumab (79).

4.2.2. Risk factors

Risk factors for ONJ include the potency, dosage and duration of exposure to BPs (52, 67, 72, 73, 80). The MRC Myeloma IX study found that the risk of ONJ with the use of zoledronic acid was 3.7% after a median follow up of 23.7 months versus 0.5% with clodronate (81). In a single centre study, the median time to development of ONJ with oral BPs, pamidronate and zoledronic acid was 54, 34 and 16 months respectively (82). Notably, the incidence increases with more prolonged exposure. Patients exposed to zoledronic acid had an incidence of ONJ of 0.5%, 1% and 1.3% at 1 year, 2 years and 3 years respectively (83). In contrast, the risk of ONJ for osteoporotic patients treated with yearly zoledronic acid was very low reflecting the low cumulative dosage of BP used (50).

Concomitant oral disease and dental procedures especially dental extractions, represent additional risk factors (51, 67, 69, 72). Badros, *et al* estimated a 9 times greater risks of ONJ after a dental extraction while Durie and colleagues found that underlying dental problems such as infection or dental extraction was found in 81% of MM patients who developed ONJ (67, 73).

Other risk factors include older age, concomitant corticosteroid use, smoking, diabetes mellitus and cyclophosphamide therapy (67, 72, 84, 85). Genetic factors are also thought to contribute with single nucleotide polymorphisms (SNPs) found within region of the genes associated with bone

turnover and collagen formation (86, 87). Furthermore, certain metabolic bone diseases may influence the predisposition to development of ONJ with one study showing that polymorphism in the farnesyl pyrophosphate synthase gene, which encodes the protein directly inhibited by BPs, resulted in a positive correlation between carrier status and ONJ (87).

4.3. Subtrochanteric and other atypical femoral fractures

An association between long term BP use and the development of atypical femoral fractures in particular subtrochanteric fractures and fractures at the femoral shaft has recently been reported (54). Of all the femoral fractures, typically 87% occur at the proximal femur with only 3% occurring at the subtrochanteric region and 5% at the femoral shaft (88). The pathogenesis is not completely understood but may be related to long term suppression of bone remodelling leading to accumulation of microdamage (89, 90). Although it may occur in patients who have not been exposed to BPs, 93.9% of cases of atypical femoral fractures have a history of long term BP use mostly for osteoporosis but a minority for malignancy (91). The majority of patients report prodromal symptoms such as groin or thigh pain before diagnosis, hence clinicians should be aware and recognize the signs of atypical femoral fractures (91).

Table 2 Summary of current international BP guidelines for myeloma

Clinical scenario	ASCO	BCSH	EMN	ESMO	IMWG
Patient selection	• Lytic lesions on plain Xrays • Compression fractures of spine from osteopenia • Osteopenia on plain Xray or BMD	• Symptomatic patients requiring treatment whether or not bone lesions evident	• Patients requiring chemotherapy • Severe osteopenia/osteoporosis • Osteolytic lesions/pathological fractures	• Stage III (Salmon-Durie) • Relapsed patients receiving chemotherapy	• Patients myeloma • Patients osteopor osteopen from mye
Choice of BP	• PAM over ZA	• ZA over PAM	• No preference PAM, ZA or clodronate	• NA	• ZA (1st (2nd) the
Duration	• 2 years in patients with responsive or SD. Further use at the discretion of treating physician • Resume on relapsed with SRE	• Reasonable to consider stopping when patient has achieved CR or VGPR and no active bone disease • Reinstituted at the time of relapse	• Continue for 2 years • Administration beyond 2 years is not recommended • Alternative is to continue at a reduced dose or decreased frequency • Resume on relapse	• Long term	• Patients CR/VGP treatme • Patients adminis 1 year years physicia
PAM infusion time	• 90 mg over ≥ 2 hours • If CrCl <30, 90 mg over 4-6 hours	• In severe renal impairment, 30 mg over 2-4 hours in consultation with a renal physician	• 90 mg 2-4 hours	• NA	• NA
Monitoring	• Serum Cr before each infusion • If renal deterioration without apparent cause, withhold until Cr returns to 10% of baseline • Monitor serum calcium, electrolytes, phosphate, magnesium • Monitor albuminuria 3-6 months by dipstick and 24 hour collection if positive • No recommendation using bone markers	• Renal function should be carefully monitored and doses reduced in line with the manufacturers' guidance	• Monitor renal function • Patients with renal impairment should have CrCl, electrolytes and albuminuria monitored • The use of bone markers is not recommended in SRE prediction or in optimizing bisphosphonate	• NA	• Monitor each infu • Monitor and urina • Discontin renal pro returns t

ASCO-American Society of Clinical Oncology, BCSH-British Committee for Standards in Haematology, BMD-bone mineral density, BP-bisphosphonate, Cr-creati
EMN-European Myeloma Network, ESMO-European Society for Medical Oncology, Hb-haemoglobin, IMWG-International Myeloma Working Group, NA-
Network, PAM-pamidronate, SD-stable disease, SRE-skeletal related events, VGPR-very good partial remission, ZA-zoledronic acid

Guidelines for the use of BPs

1. Which patients to start on BP?

Most international guidelines recommend starting BP on all symptomatic MM patients requiring chemotherapy including patients with no visible bone lesions on conventional radiology (Table 2).

In smouldering myeloma, commencing BPs has not resulted in delayed progression to symptomatic disease including development of MBD or in PFS (92, 93).

Recommendations

- **In the light of the more recent guidelines and the fact that BP may confer a survival advantage over placebo, BPs should be started on all symptomatic MM patients requiring treatment regardless of the evidence of MBD. (Grade A, Level II)**
- **At present, there is insufficient evidence to recommend routine BP use in patients with smouldering myeloma, MGUS or patients with isolated plasmacytoma. (Grade A, Level I)**

2. Choice of BP

In Australia, oral clodronate and intravenous pamidronate and zoledronic acid are reimbursed by the PBS for the treatment and prevention of MBD. Based on the MRC Myeloma IX trial that showed superior OS and PFS of patients on zoledronic acid over clodronate, both the BCSH and IMWG have recommended zoledronic acid (45). In contrast, ASCO and the Mayo clinic favour the use of pamidronate because of the lower risk of developing ONJ and similar efficacy against SRE to zoledronic acid (52, 73, 82) (See Table 2).

Oral bisphosphonates can be considered in patients who are unable to attend hospital for infusions. However, dosing recommendations have to be followed meticulously in order for it to be effective. For example, it must be taken in the morning on an empty stomach with a glass of plain water and

patients should refrain from eating, drinking or taking other drugs for at least 1 hour, otherwise absorption of the BPs may be affected (66).

Recommendations

- **Intravenous BPs are more effective than oral agents. Either pamidronate or zoledronic acid are acceptable choices for most patients. (Grade A, Level 1)**
- **The risk of ONJ is higher with zoledronic acid. In patients with increased risk of developing ONJ, pamidronate may be preferred. (Grade B, Level II)**
- **Oral clodronate is a reasonable option in patients who are unable to attend hospitals for infusion, however dosing recommendations have to be followed meticulously. (Grade D)**

3. Dosing, frequency and monitoring

Doses are recommended as in Table 3 with adjustments made for renal function. If renal function deteriorates without any other apparent causes, ASCO and IMWG guidelines recommend that BPs should be withheld until it returns to within 10% of the baseline (Table 2).

Pamidronate and zoledronic acid are not recommended below CrCl <30 ml/min and clodronate is contraindicated if CrCl <10 ml/min (94) (Table 3). However, either slowed infusion rate or reduced dose for pamidronate has been proposed by ASCO and BCSH (Table 2). In a randomized trial of either 30 mg or 90 mg pamidronate, 30 mg is as efficacious in terms of quality of life and time to first SRE. Notably, there was also a trend towards lower risks of renal toxicity and ONJ in the 30 mg group (95).

Table 3 BP dosing in renal insufficiency. ***Adapted from MIMS online(94) and Terpos 2015(96)***

Creatinine clearance (ml/min)	Recommended dose for clodronate (daily)
>80	1600 mg

50-80	1600 mg (no dose reduction)
30-50	1200 mg
10-30	800 mg
<10 or on dialysis	not recommended
Creatinine clearance (ml/min)	Recommended dose for zoledronic acid (3-4 weekly)
>60	4 mg over 15 minutes
50-60	3.5 mg over 15-30 minutes
40-49	3.3 mg over 15-30 minutes
30-39	3 mg over 15-30 minutes
<30	not recommended
Creatinine clearance (ml/min)	Recommended infusion time for pamidronate 90 mg (3-4 weekly)
>60	2-4 hours
30-60	reduce dose or infuse over 4-6 hours
<30	not recommended unless life-threatening hypercalcaemia

Recommendations

- **Pamidronate and zoledronic acid are administered every 3-4 weeks. Oral clodronate to be administered daily in 1 or divided doses. (Grade A)**
- **Renal function should be measured prior to each infusion. (Grade A). For unexplained renal deterioration, BPs should be withheld until renal function returns to within 10% of the baseline. (Grade A, Level II)**
- **In patients with renal impairment, the dose of zoledronic acid should be adjusted as per manufacturer's recommendation. (Grade C). It may also be reasonable to decrease infusion rate to 30 minutes. (Grade C, expert opinion). No similar dose reduction**

recommendation exists for pamidronate and again, it may be reasonable to either administer it over a longer duration or reduce the dose to 30 or 60 mg. (Grade C, Level IV)

- **Neither pamidronate or zoledronic acid is recommended in patients with severe renal impairment however in the case of life-threatening hypercalcaemia or significant MBD, pamidronate 30 mg over 2-4 hours may be used. (Grade C, Level IV)**
- **Serum calcium, phosphate and magnesium should be measured regularly. Patients may need calcium and Vitamin D supplementation. (Grade A, Level I). Calcium should be used cautiously in patients with renal impairment and should not be taken concurrently with oral BP.**

4. Duration

There are no data to indicate optimal duration of therapy. In the MRC Myeloma IX trial, long term follow up of patients up to 4 years on 4 weekly zoledronic acid or daily oral clodronate demonstrated low incidence of adverse events including ONJ and acute renal failure (97). Similarly, in the Z-MARK study, patients who had already received 1-2 years of prior BP therapy received either zoledronic acid 4 mg at 4 weekly or 12 weekly intervals based on the level of bone resorption marker, urinary N-telopeptide of type 1 collagen (uNTX). The rate of SRE, as well as adverse events, were low in this study and the authors concluded that the 12 weekly dosing schedule is safe and effective for up to 4 years (98).

There may be a role in using risk stratification of SRE to adjust scheduling of BP therapy (99) (see Table 4 and Figure 1).

Table 4 Risk stratification for development of further SRE. Adapted from Dickinson *et al* 2009 (99)

Risk for development of SRE	
Low	• CR or VGPR • <4 prior bone lesions and no osteoporosis

Intermediate	• SD • >4 prior bone lesions or osteoporosis • No SRE within 4 months
High	• Risk of hypercalcaemia • Progressive disease

Recommendations (See Figure 1)

- **For patients who have achieved CR or VGPR, monthly BPs should be continued for up to 2 years. (Grade D). It can then either be stopped if risk for development of further SRE is low or the frequency decreased to 3 monthly intervals if risk is intermediate. (Grade D, Level III-3). Monthly administration should be resumed at relapsed. (Grade C, Level II)**
- **For patients who do not achieve CR/VGPR but show evidence of stable disease (intermediate risk), consider decreasing frequency to 3 monthly intervals after 2 years of therapy. (Grade D, Level III-3)**
- **Patients with active or progressive disease (high risk), BPs should continue on a monthly basis. (Grade B)**

5. How to prevent ONJ?

Prior to initiation of BP therapy, except in cases where patients require immediate therapy, all the major guidelines recommend that patients should undergo a comprehensive dental examination and any existing dental problems be addressed.

For patients who must undergo major oral surgical procedures, there is little evidence to support withholding BP as it can stay in the bone for many years. However, the International Task Force on ONJ recommends interrupting BP therapy until soft tissue healing has occurred (100). The Mayo Clinic has recommended withholding BPs for at least 1 month before the procedure but the IMWG has recommended discontinuation for 90 days before and after invasive dental procedures including

extractions, dental implants and surgery to the jaw (101, 102). Prophylactic antibiotics may also be beneficial for the prevention of ONJ in patients who require invasive dental procedures (103, 104).

Recommendations (All Grade C, Level IV, except indicated)

- **Prior to initiation of BP therapy, patients should undergo a comprehensive dental examination, address any pre-existing dental problems and optimize periodontal health.**
- **Patients should be educated about the importance of dental hygiene and early recognition of symptoms. They should have regular dental check-up at least every 12 months.**
- **New dental problems should be managed conservatively and dental extractions and other surgical procedures should be avoided unless absolutely necessary.**
- **Major invasive dental procedures should be performed by an experienced oral surgeon.**
- **Prophylactic antibiotics may be beneficial in patients undergoing invasive dental procedures.**
- **For patients who require invasive dental procedures, BPs should be withheld until soft tissue healing has occurred.**
- **For patients who require invasive dental procedures, in the absence of data, it would seem reasonable to withhold BPs 1-3 months prior to the procedure taking into account the estimated risks and benefits for the individual patient. (Grade D)**

6. Management of established ONJ

ONJ is defined as the presence of exposed bone in the maxillofacial region that does not heal within eight weeks after identification by a health care professional and should be managed by an experienced oral surgeon (100, 101). BPs should be discontinued until healing occurs (102). If BPs are to be resumed, Methrotra *et al* recommends using pamidronate instead of zoledronic acid and administering it over longer intervals, as the incidence of development of ONJ is lower with the

former agent (82). Treatment is aimed at reducing pain, controlling soft tissue and bone infections and minimizing progression of bone necrosis. The majority of patients can be managed conservatively including maintenance of optimal dental hygiene with chlorhexidine mouth washes, limited debridement and antibiotics which may result in healing in 30-60% of cases (105, 106). In more established disease, surgical excision of necrotic bone may be necessary (75, 100).

Recommendations

- **Treatment of ONJ should be conservative in most cases. (Grade C, Level IV)**
- **BPs should be discontinued in patients who develop ONJ ideally until soft tissue healing occurs. However, this decision should be made on a case by case basis depending on the risk-benefit ratio especially in patients with active MM. It may be reasonable to resume therapy when there is an improvement in bone status. (Grade C, Level IV)**
- **For patients who developed ONJ while on zoledronic acid, it may be reasonable to change to pamidronate. (Grade D, Level II)**

7. Utility of bone resorption markers to guide BP therapy

Bone turnover markers measure collagen breakdown products and other molecules released from osteoblasts and osteoclasts during the process of bone resorption and formation. Bone resorption markers have been used as tools to evaluate the extent of bone disease, predict risk of SRE and also response to therapy (107).

BPs result in a rapid decrease in bone resorption markers (43, 108, 109) and there has been interest in using bone turnover markers to decide when to cease BP therapy or decide on the interval between doses. A small retrospective study found as expected serum C-terminal telopeptide of Type 1 collagen (CTX) was significantly suppressed with BP. Notably, patients with increasing levels of CTX (although still within the reference range) whilst on BP was predictive of progression of bone disease (110). However, the FLEX study did not support these findings (111). In this study, post-

menopausal women who had received 4-5 years of alendronate were further randomized to receive 5 years of alendronate or placebo. uNTX and bone specific alkaline phosphatase (b-ALP) were performed at baseline, 1 year and 3 years and the authors concluded that the bone markers did not predict fracture risks. Similarly, another study which looked at MM patients receiving either monthly or 3 monthly zoledronic acid based on levels of uNTX found that it is not predictive of SRE (98).

Serum CTX has also been proposed by some oral surgeons to assess risk and guide dental treatment in patients taking BPs (112). They proposed that a certain "cut off value" of CTX would identify patients who were at higher risk of developing ONJ. However, patients taking BPs will nearly always have low levels of CTX which can persist for many months following the discontinuation of BP therapy (98, 110). Moreover, the majority of these patients will not develop ONJ (113).

Currently, the international guidelines do not recommend the use of biochemical markers of bone metabolism to monitor the use and optimization of BPs nor in SRE risk prediction.

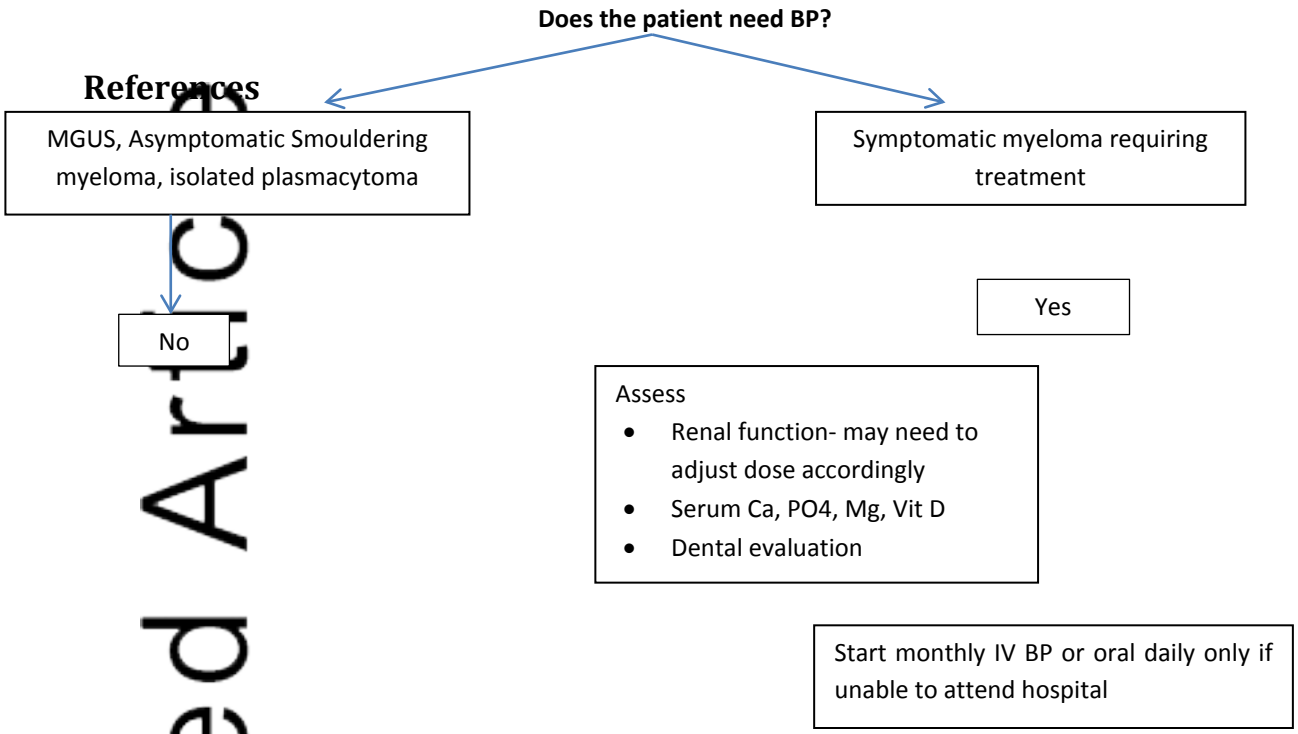
Recommendations (All Grade B)

- **Although there are studies that show that bone resorption markers are predictive of the risk of SRE, there is currently no recommendation to use them routinely.**
- **Currently, there is no role for the use of bone resorption markers in monitoring the use of BP therapy.**
- **There are insufficient data to support the use of bone resorption markers to determine the risk of ONJ in patients requiring invasive dental procedures.**

Conclusion

MBD is common and a devastating complication of MM and contributes to increased morbidity and mortality of patients. These guidelines are based on the most recent data available and aim to clarify the role of BPs in treatment and prevention of this condition. Although the use of BPs in the

management of MBD has demonstrated benefit, there are also long term consequences that need to be recognized and managed appropriately. The proposed algorithm for the use of BP in MM is shown in Figure 1.



References