review

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The use of bisphosphonates in multiple myeloma: recommendations of an expert panel on behalf of the European Myeloma Network

E. Terpos[1,2*], O. Sezer[3], P. I. Croucher[4], R. García-Sanz[5], M. Boccadoro[6], J. San Miguel[5], J. Ashcroft[7], J. Bladé[8,9], M. Cavo[10], M. Delforge[11], M.-A. Dimopoulos[1], T. Facon[12], M. Macro[13], A. Waage[14] & P. Sonneveld[15]

[1]Department of Clinical Therapeutics, University of Athens School of Medicine, Alexandra University Hospital, Athens, Greece; [2]Department of Hematology, Faculty of Medicine Imperial College London, London, UK; [3]Department of Hematology and Oncology, Charité—Universitätsmedizin Berlin, Berlin, Germany; [4]Unit of Bone Biology, Division of Clinical Sciences (South), University of Sheffield Medical School, Sheffield, UK; [5]Department of Hematology, University Hospital of Salamanca and Centro de Investigación del Cáncer, University of Salamanca, Salamanca, Spain; [6]Division of Hematology, San Giovanni Battista Hospital, Università di Torino, Turin, Italy; [7]Department of Hematology, Pinderfields Hospital, Mid-Yorkshire NHS Trust and University of Leeds, Wakefield, UK; [8]Department of Hematology, Hospital Clinic I Provincial, Barcelona; [9]Institut d'Investigacions Biomèdiques Agustí Pi i Sunyer, Barcelona, Spain; [10]Institute of Hematology and Medical Oncology ''Seràgnoli'', Bologna University School of Medicine, S.Orsola's University Hospital, Bologna, Italy; [11]Department of Hematology, University Hospital Leuven, Leuven, Belgium; [12]Service des Maladies du Sang, Hôpital Claude Huriez, CHRU, Lille; [13]Department of Clinical Hematology, Centre Hospitalier Universitaire de Caen, Caen, France; [14]Department of Hematology, St Olavs Hospital/NTNU, Trondheim, Norway and [15]Department of Hematology, Erasmus Medical Center, Rotterdam, The Netherlands

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Background: Bisphosphonates (BPs) prevent, reduce, and delay multiple myeloma (MM)-related skeletal complications. Intravenous pamidronate and zoledronic acid, and oral clodronate are used for the management of MM bone disease. The purpose of this paper is to review the current evidence for the use of BPs in MM and provide European Union-specific recommendations to support the clinical practice of treating myeloma bone disease.

Design and methods: An interdisciplinary, expert panel of specialists on MM and myeloma-related bone disease convened for a face-to-face meeting to review and assess the evidence and develop the recommendations. The panel reviewed and graded the evidence available from randomized clinical trials, clinical practice guidelines, and the body of published literature. Where published data were weak or unavailable, the panel used their own clinical experience to put forward recommendations based solely on their expert opinions.

Results: The panel recommends the use of BPs in MM patients suffering from lytic bone disease or severe osteoporosis. Intravenous administration may be preferable; however, oral administration can be considered for patients unable to make hospital visits. Dosing should follow approved indications with adjustments if necessary. In general, BPs are well tolerated, but preventive steps should be taken to avoid renal impairment and osteonecrosis of the jaw (ONJ). The panel agrees that BPs should be given for 2 years, but this may be extended if there is evidence of active myeloma bone disease. Initial therapy of ONJ should include discontinuation of BPs until healing occurs. BPs should be restarted if there is disease progression.

Conclusions: BPs are an essential component of MM therapy for minimizing skeletal morbidity. Recent retrospective data indicate that a modified dosing regimen and preventive measures can greatly reduce the incidence of ONJ.

Key words: bisphosphonates, multiple myeloma, osteonecrosis of the jaw, recommendations, renal impairment

introduction

Multiple myeloma (MM) is a malignant, hematological neoplasia of plasma cells. Affecting older adults, the median age of patients with MM at diagnosis is 65 years [1], with an incidence rate of 5.7/100 000 people in the European Union (EU) and 27 500 new cases reported each year [2]. MM is more common in men than women and accounts for ~10% of blood cancers in Caucasian populations, with a higher incidence rate in populations of African descent [3]. Age is also a major risk factor for MM: while 1% of cases occur under the age of 40 years, >50% of cases are diagnosed in people >65 years. The annual death rate is 4.1/100 000 with a 5-year survival rate of 28% [3, 4]. Recent studies have shown improvements in survival which are likely due to recent advances in MM therapies and their implementation in clinical practice [5, 6].

MM is characterized by clonal expansion of plasma cells resulting in elevated immunoglobulin levels, hypercalcemia,

Correspondence to: Dr E. Terpos, Department of Clinical Therapeutics, University of Athens School of Medicine, Alexandra University Hospital, 5 Marathonomahon Street, Drossia, 14572, Athens, Greece. Tel: +30-210-7463803; Fax: +30-210-7464676; E-mail: eterpos@hotmail.com

immunodeficiency, renal insufficiency, and lytic bone disease [7]. The disease causes symptoms of anemia, a compromised immune response leading to increased susceptibility to infections and severe pain as a result of osteolytic lesions. The destruction of bone occurs in 90% of MM patients and is the result of multiple factors [8]. Bone destruction can result in skeletal complications such as bone pain, pathological fractures requiring surgery and/or radiation to bone, spinal cord compression, and hypercalcemia of malignancy [9–11]. Recently, the impact of bone resorption activity has been confirmed as an independent risk factor in overall survival (OS) in patients with active MM [12]. Many of these complications are associated with significant morbidity and can negatively impact survival. Moreover, skeletal events compromise mobility and day-to-day independence, decrease quality of life (QoL) [13–15], and increase treatment costs [16–18]. To reduce and delay the skeletal morbidity caused by MM, bisphosphonate (BP) treatment has become the standard of care.

design and methods

manuscript development

The majority of the authors convened for a single, face-to-face meeting in June 2007 to discuss major areas of concern, identify the therapeutic issues and develop recommendations and review-associated evidence for the management of myeloma bone disease. The paper was developed in several stages: the initial draft which was created after the aforementioned meeting by Evangelos Terpos (ET) was critically revised in multiple revision rounds by all authors, until consensus was reached. The authors were selected as a panel of expert clinicians from across the EU, each contributing specific information regarding BP management of MM in their particular country, in a joint effort to produce recommendations reflecting the treatment options across the entire EU.

levels of evidence and grade of evidence for recommendations

The levels of evidence and grades of recommendation are similar to those used previously in the American Society for Clinical Oncology (ASCO) guidelines [19, 20], with the exception of level V evidence which was based on author expert opinion, in addition to case reports and clinical examples. The expert panel reviewed the evidence available from randomized clinical trials, observational studies, case reports, clinical practice guidelines, and systematic reviews of published clinical trials. In cases of paucity in the published data, the panel used their own clinical experience to support their recommendations. The evidence was ranked and the recommendations graded as follows:

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).

Level II: Evidence obtained from at least one well-designed experimental study. Randomized trials with high false-positive and/or -negative errors (low power).

Level III: Evidence obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled single-group, pre–post, cohort, time, or matched case–control series.

Level IV: Evidence from well-designed, nonexperimental studies such as comparative and correlational descriptive and case studies.

Level V: Evidence from case reports and clinical examples; expert opinion of the authors.

grade for recommendation.

Grade A: There is evidence of type I or consistent findings from multiple studies of types II, III, or IV.

Grade B: There is evidence of types II, III, or IV and findings are generally consistent.

Grade C: There is evidence of types II, III, or IV but findings are inconsistent.

Grade D: There is little or no systematic empirical evidence; recommendation decided by panel consensus based on level V evidence.

literature review

the pathophysiology of myeloma bone disease

A dramatic increase in osteoclast function, in addition to an inhibition of osteoblast ability to produce new bone, leads to the development of lytic lesions [10, 21–23]. Suppression of osteoblast precursor differentiation and induction of apoptosis in mature osteoblasts result in decreased bone formation. Increased production of molecules, such as dickkopf-1 and secreted frizzled-related protein 2, which act as Wingless-type signaling antagonists are, at least in part, responsible for the osteoblast dysfunction in MM (Figure 1) [24–26]. Other molecules such as interleukin (IL)-7 and IL-3 have been shown to inhibit osteoblastic differentiation *in vitro* [27, 28]. Furthermore, transforming growth factor β, whose release is increased by enhanced osteoclastic activity, inhibits osteoblast maturation and mineralization [29, 30]. Apoptosis of osteoblasts is mediated by increased expression of the Fas ligand and tumor necrosis factor (TNF)-related apoptosis-inducing ligand on myeloma cells, which activate the Fas receptor and the death receptor-4/5 on cells of the osteoblast lineage [31]. Osteoblast function is also impeded by the rapid growth of myeloma cells [23], which attach to bone marrow stromal cells (BMSCs; Figure 1) stimulating the production of osteoclast-activating factors such as receptor activator of nuclear factor-kappa B ligand (RANKL), macrophage colony-stimulating factor as well as an assortment of cytokines (IL-6, IL-1b, IL-11) [32, 33]. The secretion of TNFα and other cytokines into the myeloma bone microenvironment induces osteoblasts and BMSCs to produce additional RANKL and decrease the production of osteoprotegerin (Figure 1), the decoy receptor for RANKL [34–36]. Furthermore, macrophage inflammatory protein 1-alpha, hepatocyte growth factor, and vascular endothelial growth factor are increased in the bone microenvironment, further stimulating osteoclastogenesis and bone digestion [34–38]. Increased osteoclast activity can be detected by the production of type I collagen breakdown products as well as by the release osteoclast-specific enzymes (to be discussed later in this work). Further changes in the cytokine milieu also contribute to bone loss (Figure 1) [10, 21, 23, 30, 39–41].

BPs and their mechanism of action

BPs are synthetic, stable analogues of inorganic pyrophosphate (PPi) [42]. Unlike PPis, BPs are stable and resistant to hydrolysis by blood phosphatases [43]. Their affinity to Ca^{2+}

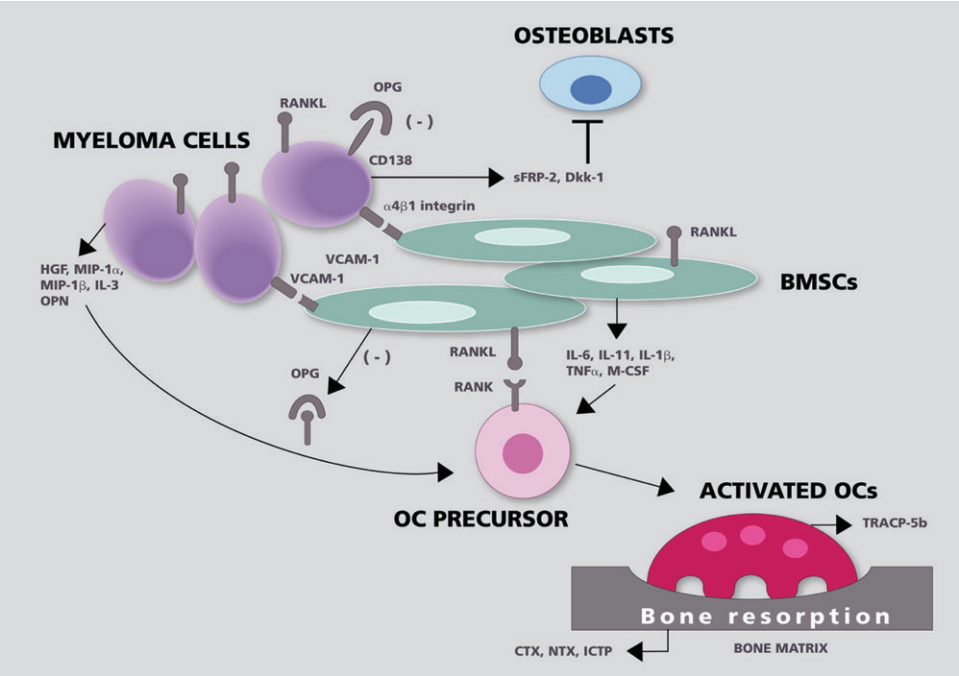

Figure 1. Overproduction of cytokines with osteoclast activation function results from interaction between myeloma cells and bone marrow stromal cells (BMSCs). Interleukin (IL)-6, IL-11, IL-1β, macrophage colony-stimulating factor (M-CSF), and tumor necrosis factor-α (TNFα) are produced predominantly by BMSCs, while hepatocyte growth factor (HGF), macrophage inflammatory protein (MIP)-1α, MIP-1β, IL-3, and osteopontin (OPN) are primarily produced by myeloma cells. Receptor activator of nuclear factor-kappa B ligand (RANKL), a potent activator of osteoclasts, is overproduced in the bone marrow microenvironment of multiple myeloma patients, while production of OPG, the soluble decoy receptor for RANKL, is reduced in BMSCs inhabiting the myeloma marrow setting. Simultaneously, myeloma cells internalize and degrade OPG via CD138 (sydecan-1). The ratio of RANKL/OPG is skewed in favor of RANKL, resulting in increased osteoclastogenesis and osteoclast function. Bone resorption produces degradation products of type I collagen (NTX, CTX, ICTP) that can be quantified in the urine or the serum. Tartarate-resistant acid phosophatase isoform 5b (TRACP-5b) is also produced by osteoclasts. In addition to increasing resorption, myeloma cells inhibit osteoblast differentiation and function, by producing molecules such as dickkopf-1 (Dkk-1) and secreted frizzled-related protein 2 (sFRP-2). This cycle is self-perpetuating as myeloma cells derive a survival benefit from the increased osteoclast activation via IL-6 production or other unidentified mechanisms. Adapted from Terpos et al. [22].

allows them to bind quickly and specifically to hydroxyapatite, the major calcium-containing mineral in bone, especially in regions where resorption is occurring. When osteoclasts break down bone, BPs accumulate in the resorption space under these cells, exposing them to high BP concentrations [44, 45].

There are two main types of BPs, nitrogen and non-nitrogen containing, each of which has a different mechanism of action for preventing bone resorption. The first generation of BPs are non-nitrogen-containing compounds such as etidronate (ETI) and clodronate (CLO) which are metabolized to cytotoxic ATP analogues, which induce osteoclast cell death [46–48]. The more recently developed nitrogen-containing BPs (N-BPs) such as ibandronate (IBA), risedronate (RIS), pamidronate (PAM), and zoledronic acid (ZOL) have a much greater potency *in vitro* than compounds such as ETI and CLO [49]. N-BPs bind and inhibit the enzyme farnesyl pyrophosphate synthase, in the mevalonate pathway, disrupting the formation of farnesyl diphosphate and geranylgeranyl diphosphate [50–52]. These molecules are involved in prenylation, a post-translational modification of proteins, tethering them to the cell membrane with a hydrophobic anchor [53]. This process is critical for allowing proteins to be localized to the appropriate parts of the cell in order to mediate their biological activity. This is important for the activity of a range of proteins including the small GTPases, Ras, Rac, and Rho, which play key roles in regulating osteoclast function and events in bone resorption [54].

clinical evidence for the effectiveness in BP treatment of MM

Table 1 summarizes the results of several studies which examine the treatment of MM patients with BPs. ETI showed a lack of effectiveness in preventing skeletal-related events (SREs), bone pain, and fracture [55, 56]. IBA also failed to show any effect on bone morbidity and in prolonging patient survival [63].

CLO has been shown to reduce the development of new osteolytic lesions by 50% after 2 years of administration, as well as to reduce the degree of hypercalcemia and hypercalciuria, and to decrease bone pain (24% versus 12%; $P = 0.026$) [57]. Another study concluded that there was no difference in OS of MM patients treated with CLO [58]; however, after a 1-year follow-up, there was a reduction in fracture rate (13.2% versus 6.8%; $P = 0.04$) as well as in the time to the first nonvertebral fracture [17]. Among the subgroup of patients without skeletal fractures at presentation, there was a significant survival advantage ($P = 0.006$) in favor of patients receiving CLO, with median survival time reported as 59 months [95%

Table 1. Major double-blind trials of BPs in MM

Authors and year	Type of BP	Dosage	No. of MM patients	Reduction of pain	Reduction of SREs[a]	Survival benefit
Placebo controlled						
Belch et al. (1991) [55]	Etidronate	5 mg/kg/day, p.o.	173	No	No	No
Daragon et al. (1993) [56]	Etidronate	10 mg/kg/day, p.o., for 4 months	94	No	No	No
Lahtinen et al. (1992) [57] and Laakso et al. (1994) [58]	CLO	2.4 g/day, p.o., for 2 years	350	Yes	Yes	NE
McCloskey et al. (1998) [17] and (2001) [59]	CLO	1.6 g/day, p.o.	530	Yes	Yes	+/−[b]
Brincker et al. (1998) [60]	PAM	300 mg/day, p.o.	300	Yes	No	No
Berenson et al. (1996) [61] and (1998) [62]	PAM	90 mg, i.v., every 4 weeks for 21 cycles	392	Yes	Yes	+/−[c]
Menssen et al. (2002) [63]	Ibandronate	2 mg, i.v., monthly	198	No	No	No
PAM controlled						
Berenson et al. (2001) [64][d]	ZOL	2 or 4 mg, i.v., monthly	108	Yes	Yes	NE
Rosen et al. (2001) [65] and (2003) [66][d]	ZOL	4 or 8 mg, i.v., monthly	513	Yes	Yes	[e]

[a]SREs denote skeletal-related events: new lytic lesions, vertebral and nonvertebral fractures, and need for radiation or surgery to the bone.
[b]In a *post hoc* analysis, patients without vertebral fracture at entry survived significantly longer on CLO (median survival was 23 months longer than in similar patients receiving placebo).
[c]Survival in the patients with more advanced disease was significantly increased in the PAM group (median survival 21 versus 14 months; $P = 0.041$ adjusted for baseline serum β2-microglobulin and Eastern Cooperative Oncology Group performance status).
[d]PAM-controlled trial.
[e]Survival benefit with zoledronic acid over PAM for a subgroup of patients who had elevated baseline bone-specific alkaline phosphatase levels.
BPs, bisphosphonates; MM, multiple myeloma; PAM, pamidronate; ZOL, zoledronic acid; CLO, clodronate; NE, not evaluated.

confidence interval (CI) 43–71 months] and 37 months (95% CI 31–52 months) and 5-year survivals of 46% and 35%, respectively [59]. At 2 years, the CLO-treated patients also had less myeloma-related pain than patients treated with placebo [59]. However, in a Finnish study [57], the oral CLO group did not experience a significant reduction in vertebral fractures. No studies have yet compared CLO directly with other BPs.

A PAM-based study of MM patients who were entered in a randomized study to receive either oral PAM or placebo showed no reduction in SREs, likely due to the low absorption of orally administered PAM [60]. In another PAM trial, patients with lytic lesions, who were randomized to placebo or i.v. PAM, showed a reduced number of SREs and a decrease in the time to the first skeletal event in the PAM group (41% versus 24%; $P < 0.001$) [61]. While there were no differences in survival time in the treatment groups, a subgroup of patients who had received more than one previous antimyeloma treatment displayed increased survival time (14 versus 21 months, $P = 0.041$). In addition, pain scores and QoL were improved in the PAM group [62].

A phase II trial comparing ZOL and PAM showed that both BPs significantly reduced SREs, and a large, phase III trial showed an increase in time to first SRE in both groups [64, 65]. The skeletal morbidity rate and normalization of the bone resorption marker, N-telopeptide of collagen type I (NTX), were improved in the ZOL group [65]. 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% ($P = 0.025$), while confirming the similar efficacies of ZOL and PAM in MM patients [66]. Based on these studies, BPs appear to be effective in preventing the development of osteolytic bone disease in patients with myeloma and have become key agents in treating MM patients.

current guidelines for BP use in MM

Current guidelines for BP treatment of MM have been compiled by the National Comprehensive Cancer Network [67], the ASCO [68], the Mayo Clinic [69], the European Society for Medical Oncology [70] and the International Myeloma Working Group [71] and are summarized in Table 2.

bisphosphonate therapy: benefits and limitations

The choice of a BP in treating myeloma bone disease is defined by several factors including efficacy, patient compliance, choice of route of administration, safety profile as well as cost and availability.

results

efficacy of BP therapy

The *in vivo* efficacy of BPs seems to correlate with the *in vitro* potency. Generally, with regards to potency, ETI < CLO < PAM < ALE < RIS < IBA < ZOL [72, 73]. Of these, only CLO, PAM and ZOL have been approved for use in MM patients in Europe, and CLO is not approved in many EU countries. Assessment of SREs, such as pathological fracture, radiation therapy, and surgery to bone, hypercalcemia, and

Table 2. Summary of recent MM guidelines

Clinical scenario	NCCN [67]	ESMO [70]	ASCO [68]	MAYO [69]	IMWG reply to MAYO [71]	EMN (this publication)
Patient population	Active or all other stages of myeloma Adjunctive treatment for bone disease	Stage III or relapsed disease receiving conventional-dose CT	Lytic disease on plain radiographs Patients with osteopenia based on normal plain radiograph or BMD measurements	All patients with lytic bone disease on plain radiographs; patients with osteopenia or osteoporosis on BMD studies	In addition to radiographs, other imaging studies (MRI, CT and CT/PET)	All patients with lytic bone disease on plain radiographs; patients with osteopenia or osteoporosis on BMD studies; patients on chemotherapy
Administration	i.v.	p.o. or i.v.	p.o. or i.v.	i.v.	i.v. or p.o.	i.v. or p.o.
PAM i.v. infusion time	N/A	N/A	At least 2 h	At least 2 h	N/A	2–4 h
Duration/frequency	N/A	Long term	Monthly for 2 years	Monthly for 2 years After 2 years Discontinue if CR or stable plateau phase ↓ to every 3 months if active disease	2 years. After 1 year: Discontinue if CR or VGPR and no active bone disease Continue if below VGPR (<VGPR) and/or ongoing active bone disease After 2 years Discontinue if no active bone disease If active bone disease, continue at own discretion	2 years. After 1 year: Continue at physicians discretion Restart upon relapse
Monitoring	Chronic users should be monitored for renal function and ONJ	N/A	Monitor serum creatinine before each PAM or ZOL dose	N/A	N/A	Monitor patients for compromised renal function (creatinine clearance)
	Smoldering/stage I MM use BP in a trial with yearly bone surveys		Regularly monitor serum calcium, electrolytes, phosphate, magnesium, hematocrit/hemoglobin			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 (favored) 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; COL, clodronate.

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spinal cord compression, is common end points in clinical trials of BPs in cancer treatment [61]. Impact on bone pain and bone resorption markers is also often examined as secondary end points.

recommendations. There is strong evidence to recommend BP therapy as a component of the disease treatment of MM patients with either osteolytic bone lesions (grade A) or osteopenia (grade C).

pain control with BPs

The majority of MM patients suffer debilitating pain due to osteolytic bone disease [13, 74]. Reduction and control of pain is a crucial aspect in maintaining a high QoL. BPs have been shown to reduce bone pain and maintain it at a lower level, improve QoL in myeloma patients, and reduce analgesic consumption though it is uncertain if this effect is a direct one or if it is due to amelioration of bone disease [17, 61, 75, 76]. Pain is one of the most distressing symptoms of MM, and pain control is deemed by the panel as being as important as prolonging OS in order to preserve QoL. Analgesia should be used in conjunction with BP therapy and geared toward World Health Organization (WHO) stepwise escalation guidelines: the panel agrees that 'if pain occurs, there should be prompt oral administration of drugs in the following order: nonopioids (aspirin and paracetamol); then, as necessary, mild opioids (codeine); then strong opioids such as morphine, until the patient is free of pain. To calm fears and anxiety, additional drugs—"adjuvants"—should be used. To maintain freedom from pain, drugs should be given "by the clock", that is every 3–6 hours, rather than "on demand". This three-step approach of administering the right drug in the right dose at the right time is inexpensive and 80–90% effective. Surgical intervention on appropriate nerves may provide further pain relief if drugs are not wholly effective' [77]. Vertebroplasty and kyphoplasty can also provide pain relief for patients with intractable spinal pain secondary to compression fractures from MM [78–80]. Pain and QoL assessment have been, until recently, done with tests developed for cancer patients considered globally. Specific tools for measuring QoL in cancers associated with a high level of bone complications, such as MM, have recently been developed in order to better assess bone pain and QoL changes [15]. A tool is also currently being developed by the European Organization for the Research and Treatment of Cancer (EORTC) with the goal of producing a robust scale for assessing QoL issues which are insufficiently covered by the EORTC core questionnaire, with a focus on cancer patients with bone metastases [81].

recommendations. Intravenous ZOL, PAM, or oral CLO are useful in the control of bone pain due to myeloma bone disease; however, analgesia should be used in conjunction with BP therapy, in accordance with the WHO recommendations (grade B).

adherence to BP therapy

BPs effectively reduce and delay skeletal complications in MM provided their dosing recommendations are adhered to [22, 82]. It is essential that all patients prescribed a BP are informed of the crucial importance of adherence to the recommended dosing regimen. CLO is administered orally in a 1600-mg single dose or in two divided doses (800 mg). The tablets should be taken on an empty stomach with fluid (not milk) at least 1 h before or 1 h after food, on a daily basis, in order to maximize bioavailability which is low, in the range of 2% [83]. Despite this CLO remains an effective agent in the management of bone disease in MM. Some randomized placebo-controlled trials of CLO in MM suggest that long-term compliance is satisfactory [17, 57]; however, in studies of BPs prescribed for osteoporosis and metastatic bone disease, dosing compliance was poor, especially with daily or weekly dosing schedules [84–87]. This low level of compliance also occurs in BP treatment of bone metastases in breast and prostate cancer patient populations [88, 89] and could interfere with treatment efficiency. There is a majority agreement within the panel that compliance with oral BPs may be suboptimal. Infusion of BPs has the advantage of greater levels of compliance; however, administration requires medical personnel present whether the drug is given in the clinic or at home [89]. The shorter infusion time (15 min) required for ZOL as compared with other BPs allows for administration with less disruption for the patient than the 2–4 h time required for infusion of PAM. A study comparing patient preference for either ZOL or PAM showed a 92% preference for ZOL due to the shorter infusion time [90].

recommendations. Patients must be educated in the need for adherence to dosing requirements (grade D). Due to the potential compliance problems with oral BPs, i.v. administration of BPs may be preferable (grade D).

choice of BP and administration route

BP therapy has been shown to be beneficial in the treatment of various cancers that cause metastatic bone disease [66, 91–97]. The choice of BP treatment used in MM varies according to country. ZOL is the BP used most frequently in many EU countries. Oral administration (CLO) is also an option for patients who cannot receive regular hospital care, and it is frequently used in UK and Finland. For effective response to oral BPs, dosing recommendations must be scrupulously followed and precautions taken to avoid potential gastrointestinal (GI) adverse events (AEs) [98]. Furthermore, oral CLO has not been approved in all EU countries for MM patients. Intravenous delivery of BPs (PAM and ZOL) is generally carried out as an outpatient procedure in a clinical environment ensuring compliance. As mentioned above, it can be combined with the clinical monitoring of patients. Infusion time ranges from 15 min (ZOL) to 2–4 h (PAM). For patients where administration at the outpatient clinic is not possible, home visits for i.v. infusion of BPs have been shown to significantly improve the QoL of breast cancer patients with bone metastatic disease [99] and might be a suitable option for MM.

recommendations. Intravenous ZOL and PAM are equally effective in terms of reducing SREs in MM (grade B). Home i.v. infusion or oral BPs can be considered (where feasible and approved) for patients who cannot attend hospital visits (grade D).

dosing and initiation of BP therapy

Before any BP treatment of MM is undertaken, it is important to monitor the patients for compromised renal function. Mild-to-moderate renal impairment, as defined by a creatinine clearance (CrCl) of 30–60 ml/min, requires reduced doses of CLO and ZOL [100, 101]. Oral CLO is not recommended below CrCl rates of 12 ml/min. PAM and ZOL are not recommended for CrCl rates <30 ml/min [101, 102]. The changes in dosing and infusion time are listed in Table 3. A randomized, double-blind trial in patients newly diagnosed with symptomatic MM suggests that 30 and 90 mg of PAM may have equal effects with respect to QoL and time to first SRE [102]. The primary end point of the trial was physical functioning at 12 months as measured by the EORTC QLQ-C30 QoL questionnaire, while secondary end points were skeletal events, cost–utility analysis, myeloma response, duration of response, survival, fatigue, and pain. The initial analysis of the QLQ data showed improvement of health status, pain, fatigue, and physical function as reported in earlier publications, but no significant difference between the two treatment arms. The authors recommend that the dose and type of BP should be reconsidered in the prophylactic treatment of newly diagnosed MM. The prospect of giving a lower dose of PAM perhaps in one-third of the infusion time merits further study, but until these results are confirmed, the majority of the expert panel recommends that BPs should always be prescribed at the manufacturer's recommended dose.

The question of the optimal time point for initiation of BP treatment has not been well studied. The panel recommends starting BP therapy upon detection of severe osteopenia or after lytic lesions of the bone have been identified. Currently, since BPs have not demonstrated any clear advantages in terms of progression-free survival in asymptomatic plasma cell dyscrasias, BPs are not recommended in Monoclonal gammopathy of undetermined significance (MGUS), solitary plasmacytoma or asymptomatic MM [103, 104]. The panel agrees that BPs should be administered in cases of radiological detection of lytic lesions, as well as in patients with severe osteopenia, irrespective of the presence of bone lesions. Further studies are needed to clarify whether it is preferable to start BP therapy at an earlier time point.

recommendations. BPs are not recommended to treat MGUS or asymptomatic MM (grade C). BPs should be administered upon detection of severe osteopenia/osteoporosis (grade C) as well as in patients with osteolytic lesions and/or pathological fractures (grade A). In the absence of visible bone lesions on plain films, if the patient requires chemotherapy, then BP treatment should be initiated (grade B).

Table 3. Bisphosphonate dosing and renal insufficiency

Creatinine clearance rate (ml/min)	Recommended dosage of clodronate (1600 mg)
>80	100%
50–80	75%
12–50	50%–75%
<12	50% or discontinue
Creatinine clearance rate (ml/min)	**Recommended dosage of zoledronic acid (mg)**
>60	4.0
50–60	3.5
40–49	3.3
30–39	3.0
<30	Not recommended
Creatinine clearance rate (ml/min)	**Recommended infusion time for pamidronate (90 mg/500 ml normal saline i.v.)**
>30	2–4 h
<30	Not recommended

synergism of concomitant BP therapy given with antimyeloma therapy

Studies on myeloma cell lines have shown that N-BPs, either alone or in combination with antimyeloma agents, have antitumor effects *in vitro* [105–110]. BPs induce significant expansion of γδT cells and exhibit specific cytotoxicity against myeloma cells [111]. Studies showed that BPs stimulating γδT cells have pronounced effects on the immune system, which might contribute to the antitumor effects of these drugs. In addition, work focused on animal models of MM suggests that myeloma cells may be dependent on osteoclast activity and vice versa [112, 113]. Furthermore, ZOL has been shown to prevent the development of osteolytic bone disease and decrease bone tumor burden in bone in an established MM animal model [114]. PAM has also shown antimyeloma activity in animal models *in vivo* [115, 116]. In contrast, IBA has failed to show antimyeloma activity *in vivo* in several animal model systems [117–119]. The relevance and validity of these preclinical findings for patient treatment is unknown at this time. ZOL or PAM in combination with conventional or novel antimyeloma agents reduce markers of bone resorption and osteoclast activators in myeloma patients in several studies [22, 76, 120–125]. Currently, there is no evidence to suggest that these are direct antimyeloma effects or if they are also due to changes in the supporting bone microenvironment.

recommendations. ZOL and PAM may have synergistic or additive effects with MM therapy and might successfully be used in conjunction with other antimyeloma agents in the future; however, there was agreement in the panel that it is premature to transfer this concept to the clinic without further clinical study (grade D).

AEs associated with BP therapy

BP therapy of MM is generally well tolerated [126]; however, patients should be made aware of potential AEs and be taught to recognize, record, and report the occurrence of these AEs and their severity. Furthermore, physicians should be proactive in asking patients about AE symptoms as well as in monitoring typical indicators of serious problems. Potential AEs from BP therapy for MM include GI ailments from oral administration, inflammatory reactions at the injection site, acute phase reactions following i.v. use, hyperthermia and hypocalcemia. Additionally, renal impairment and avascular osteonecrosis of the jaw (ONJ) are infrequent but serious complications can result from BP therapy.

GI complications of oral BPs are primarily minor and include diarrhea, nausea, and abdominal pain [57, 127, 128]. More serious GI problems such as esophagitis and ulceration have also been reported, but are uncommon [129, 130]. In order to minimize GI complications, patients should comply with dosing directions for oral BPs [100, 131].

Inflammatory reactions at the injection site of i.v. administered BPs can involve pain, swelling, and phlebitis. Acute phase reactions, characterized by influenza-like symptoms such as fever, nausea, and muscle, bone, and joint pain, can also occur, often after the first treatment and almost exclusively with N-BPs [66, 92, 132, 133]. These reactions generally resolve on their own within 3 days, and treatment of symptoms with nonprescription analgesics like paracetamol is generally sufficient to manage them [73, 134].

Hypocalcemia and hypophosphatemia can also result from BP treatment [135]. MM patients are much less likely to have symptomatic hypocalcemia as compared with solid tumor patients. Hypocalcemia is relatively mild and asymptomatic in the majority of patients suffering from MM; although severe adverse effects have been published in occasional cases [136–138], these are often preventable by treatment with oral calcium and vitamin D_3. For patients living in areas with reduced exposure to the sun, the panel recommends the routine administration of calcium (600 mg/day) and vitamin D_3 (400 IU/day) supplements.

Infusion BPs have the potential to cause both acute and chronic renal failure [139]. While acute renal dysfunction may be clinically reversible, permanent kidney damage due to acute tubular necrosis may remain and can lead to chronic renal failure [140, 141]. Development of renal difficulties can be monitored by testing serum creatinine before each dose of i.v. BP. Patients encountering such problems should be taken off BP treatment until serum creatinine returns to within 10% of its baseline level. Renal damage is dependent on the concentration of BPs in the blood, and the risk is highest during high dosage or rapid infusions [65, 142, 143]. The high affinity of BPs for metal ions induces formation of insoluble aggregates that block the renal capillaries [144]. In cases of solid tumor metastasis, it has been recommended that persistent renal deterioration be dealt with by resuming BP therapy either under reduced dosing conditions or slower infusion, both under close clinical monitoring [73]. This option could also be considered in MM.

While ZOL and PAM have similar renal safety profiles [66], IBA has the lowest level of nephrotoxicity of all the BPs [145, 146]; however, it is not licensed for treatment of MM in the EU. Oral CLO is contraindicated in patients with moderate-to-severe renal failure [100] and high-dose i.v. CLO can also cause severe renal toxicity unless infused slowly over 2–4 h [147, 148]. Adherence to the recommended infusion protocols with regards to time, dosage, serum creatinine levels, and hydration is mandatory in order to minimize the potential for renal damage. In addition to renal failure resulting from acute tubular necrosis, PAM has been associated with nephrotic syndrome due to a collapsing variant of focal segmental glomerulosclerosis, which can lead to end-stage renal disease [149, 150]. Early diagnosis is crucial for these patients and it has been recommended that albuminuria should be monitored in addition to serum electrolytes and creatinine. ZOL is not suitable for patients with severe renal impairment. Patients with a CrCl of 30–60 ml/min are considered to have mild-to-moderate renal impairment and should receive reduced doses of ZOL, with no changes in infusion time (Table 3). The majority panel recommends an infusion duration of over 4 h when using PAM in patients with renal impairment. Use of PAM in patients with a CrCl rate of <30 ml/min is not recommended (Table 3). While no reduced dosing guidelines are available for PAM, the panel agrees that clinicians should consider reducing the initial PAM dose in patients with preexisting renal impairment. While consensus could not be reached on this point, some members of the panel infuse PAM at 30–60 mg in between 2 and 4 h.

recommendations. Oral administration of BPs requires patients to take appropriate precautions to avoid GI complications (diarrhea, nausea, and abdominal pain) (grade A). Transient acute phase reactions can be managed with therapeutic analgesics and are no reason for discontinuation (grade B). Calcium and vitamin D_3 treatment should be considered to prevent electrolytic imbalance (grade B). Patients with renal impairment should have CrCl rates, serum electrolytes, and albuminuria monitored (grade B). They should receive longer infusions of lower doses of BPs (grade C). Choice of a BP with an optimal renal tolerability is recommended in patients with renal complications as described above (grade D).

osteonecrosis of the jaw

ONJ is an uncommon but potentially serious complication of i.v. BPs, which is characterized by the presence of exposed bone in the mouth. While *Actinomyces* species are frequently found in these lesions, the cause of ONJ is uncertain and likely multifactorial [151, 152]. Two of the major risk factors for ONJ are treatment with BPs and dental procedures/trauma [153–156]. The risk for ONJ increases with BP treatment duration and has been shown to be 5%–15% at 4 years [157–159]. Although ONJ has been described during the therapy with any BP, the possibility of developing ONJ may also increase with the use of the more potent BPs, with a higher incidence for ZOL [157–165] and a lower risk of developing ONJ in patients treated with PAM [157, 160]. A retrospective study of MM patients treated with ZOL on a reduced schedule (infusion every 3 months versus monthly) showed a decrease in levels of ONJ [166]. Further study is required to ensure that delivery of BPs at a reduced schedule is equally efficacious as the recommended schedule as well as to confirm the validity of the reduction in ONJ occurrence. While cases of ONJ have been reported for patients treated with oral CLO, these are very uncommon [162, 167].

Recently, guidelines for the prevention, diagnosis, and management of ONJ have been released by both the Mayo Clinic and the ASCO [68, 69]. In agreement with these guidelines, a prevention-based strategy was recommended by the panel. As the majority of ONJ cases occur after dental surgery [131, 168, 169], MM patients should receive a comprehensive dental examination before treatment with BPs, in order to identify and treat dental problems that may require surgical or invasive dental procedures. Existing

infections should be treated, and areas at high risk for oral infection over the course of BP therapy should be eliminated. Any treatment of such conditions should be completed before initiating BP therapy. Two recent studies of patients with MM or solid tumors showed that appropriate preventive measures, such as a detailed assessment of dental status by experienced specialists, and avoidance of invasive dental procedures during treatment with ZOL had the potential to greatly reduce the number of ONJ cases [170, 171]. The first study included 128 patients with MM divided into two groups: group A, with no special precautions ($n = 38$) and group B, with a detailed dental assessment and preemptive dental care ($n = 90$). The incidence rate of ONJ occurrence was 0.671/100 person-month for group A and 0.230/100 person-month for group B, a significant, threefold reduction of ONJ occurrence (information ratio 2.92, $P = 0.029$, 95% CI 1.06–8.03) [172]. The second study included ~1000 patients with solid tumors, mostly breast cancer. Twenty-five percent were given ZOL, 62% PAM, 8% PAM followed by ZOL, and 5% CLO. ONJ was observed in 28 patients (2.9%); a 75% reduction in the incidence of ONJ (from 3.2% to 1.3%) has been observed upon implementation of preventative dentistry and oral hygiene [170]. The issue of oral and dental hygiene in MM patients being treated with BPs is exceptionally important in preventing ONJ and the seriousness of preventative dental care should be discussed personally with each patient.

What evidence exists for restarting BPs in cases of ONJ healing? In a recent, long-term follow-up study of 97 myeloma patients with ONJ patients in whom ONJ was precipitated by dental procedures were less likely to have recurrence or nonhealing lesions, after BP reinitiation following ONJ healing, as compared with those who develop spontaneous ONJ lesions [169]. ONJ recurrence was linked to BP rechallenge, mostly in the setting of relapsed MM; however, BPs should be stopped if the patient develops ONJ and only reinitiated if the benefit of treating bone disease surpasses the risk of progressive ONJ. Furthermore, the authors stated that some nonhealing ONJ lesions could be chronic and remain stable over time without extensive intervention [158, 159, 169]. The reinitiation of BPs after ONJ has healed may be considered in patients with active myeloma bone disease and previous skeletal events at physician's discretion.

During BP treatment, dental status should be monitored at least on an annual basis, good oral hygiene maintained, and elective dental procedures avoided. While the preventative measures for ONJ were deemed acceptable, the majority of experts viewed the guidelines for treating existing cases of ONJ as suboptimal. In addition to the current guidelines, information on the ongoing dental status of MM patients on BP therapy needs to be communicated to their hematologist/oncologist. Where dental procedures are required, patients should be treated conservatively, minimizing invasive procedures. Furthermore, until healing of unavoidable, invasive dental procedures is complete, postponement of BP therapy should be considered. There is a paucity of data to propose a recommendation, so any decision to suspend BP treatment should be considered on a case-by-case basis. Recent data indicate that antibiotic prophylaxis may also be beneficial in preventing ONJ in BP-treated MM patients who have no choice but to undergo dental surgery [171]. Future studies to optimize BP delivery schedules and dosing in MM will no doubt reduce the number of cases of ONJ.

recommendations. Patients should receive a comprehensive dental examination and be educated regarding optimal dental hygiene (grade C). Existing/high-risk dental conditions should be treated before initiating BP therapy (grade C). After therapy initiation, unnecessary invasive dental procedures should be avoided and dental status should be monitored on an annual basis (grade D). Ongoing dental health status of patients should be followed by a physician and a dentist, preferably in communication with each other (grade D). Essential dental procedures should be managed conservatively (grade C). Temporary suspension of BP treatment should be considered if invasive dental procedures are necessary (grade D). Initial therapy of ONJ should include discontinuation of BP until healing occurs (grade C). The decision to restart BP should be individualized, until prospective long-term studies are available (grade D). The physician has to take into consideration the advantages and disadvantages of BPs mainly in the relapsed/refractory setting (grade D).

duration of BP therapy

The duration of BP therapy varies by country. The majority of the panel agrees that BP therapy should be continued for 2 years. In patients with a complete or partial remission after autologous stem cell transplantation (ASCT), most of the panelists continue BP treatment for 2 years. However, a few stop after 12 months, based on a study in 44 MM patients in remission after chemotherapy in whom lumbar spine Bone mineral density (BMD) progressively increased after a mean follow-up of 3 years; these patients never received BPs, so this increase was related to the antimyeloma treatment [173]. Use of PAM alone, as a maintenance therapy, was found to be ineffective in patients who have had high-dose therapy (HDT) followed by ASCT when used over a median time of 29 months [174]. There is currently no data for patients who achieve complete response with any treatment other than HDT. Accordingly, these patients should receive BPs as long as other patients treated without HDT: 2 years. Administration of BPs beyond 2 years is not recommended; however, some patients might still benefit from longer treatment. To date, there is no hard data to support this due to a lack of subgroup definition with different risks and consequent subgroup analysis. As an alternative to stopping BPs after 2 years, some panel members prefer to continue BP therapy at either a reduced dose or reduced schedule [102, 166]. With regard to the ASCO recommendation that, after completion of a 2-year course of BP therapy, treatment with BPs should be resumed upon onset of new SRE, the majority of experts said they would reinitiate BP therapy only in patients with pain or progression in bone. Active MM, with increasing bone pain, even in the absence of new SREs, may indicate a relapse or progression in bone involvement. A full, radiographic skeletal survey is needed to confirm whether myeloma bone progression has occurred. If progression is confirmed, all experts agree that BPs should be reinitiated.

recommendations. BPs should be given for 2 years and after that at the physician's discretion (grade D). BP therapy should be resumed upon relapse (grade D).

use of bone markers and imaging in BP therapy

Cohorts of MM patients do show bone marker changes in a variety of studies, and the idea of predicative bone marker analysis is a promising one and may play a role in future determination of BP therapy assessment. The majority of biochemical markers of bone resorption [i.e. N- or C-terminal cross-linking telopeptide of collagen type I (NTX, ICTP) and 5b isoenzyme of tartrate-resistant acid phosphatase] are elevated in MM patients with lytic bone lesions, thus reflecting changes in bone metabolism associated with tumor growth [76, 122, 173, 175–181]. There is also a growing body of evidence that markers of bone metabolism correlate with the risk of skeletal complications, disease progression, and death in MM [173, 176–179]. Furthermore, the bone resorption marker ICTP is shown to be an independent prognostic factor in myeloma patients in a multivariate model, which included parameters of International Staging System [12].

Several studies have reported that markers of bone resorption are reduced after BP therapy [66, 76, 122, 175]. Treatment with ZOL has been shown to reduce the levels of NTX more efficiently than PAM in MM [66]. This type of analysis could potentially be used as a tool for early diagnosis of bone lesions and disease progression [176–179, 182]. For these reasons, large prospective studies are ongoing to determine the optimal use of bone markers to monitor response to antiresorptive therapy and tailor treatment regimens. Bone markers might help identify patients who could obtain a survival benefit from a particular treatment. A retrospective analysis of MM patients with bone lesions was carried out in a large randomized, controlled trial of 4 mg ZOL versus 90 mg PAM to determine the effect of ZOL on survival based on baseline bone-specific alkaline phosphatase (BALP) levels. The drugs were administered every 3 or 4 weeks for up to 24 months, with a final assessment at 25 months. Among patients with high baseline BALP (≥146 U/l), ZOL significantly improved survival compared with PAM (82% versus 53%) and significantly reduced the risk of death in both univariate and multivariate analyses [179]. Several publications have recently demonstrated the impact of the novel agent bortezomib on bone markers and its possible impact on bone healing [120, 183–185].

Appropriate use of imaging techniques is essential in the identification and characterization of the skeletal complications resulting from MM. The role of imaging in assessment of MM-related skeletal complications involves determination of the extent of intramedullary bone disease, detection of extramedullary foci, and evaluation of the extent and progression of the disease. MM treatment lacks a standardized, collectively adopted imaging protocol for both newly diagnosed myeloma patients and following disease progression [186]. Lytic lesions are present in 90% of MM patients [8] and are generally diagnosed by radiographic analysis. One weakness of radiographic detection is that it may only reveal lytic disease when over half of the trabecular bone has been lost [187]. This results in a weak assessment of the generalized osteopenia that affects MM sufferers. Osteoporosis in the general population is currently diagnosed using DEXA. In MM patients, reduced lumbar spine bone mineral density is correlated with an increased risk of early vertebral collapse. This makes DEXA an important test to consider as it may influence the decision to begin BP treatment. The spine is a common site of bone complications in MM patients and suspected spinal cord compression needs to be assessed as quickly as possible. Following initial radiographic assessment of the patient, in cases with neurological symptoms, analysis of the soft tissue for damage requires additional imaging such as computed tomography or magnetic resonance imaging (MRI). MRI is the preferred imaging method as it allows accurate appraisal of bone marrow, epidural, and intradural spaces as well as the spinal cord; however, it is expensive and not always available. While providing the best assessment of neurological compromise, MRI is not required for many MM patients and is unnecessary to follow disease progression in most cases. Radiographic monitoring of lytic lesions seldom shows any change even in patients experiencing total remission, making it of little value in assessing disease response. As development of new bone lesions can indicate disease progression, any MM patient presenting with new pain or neurological symptoms due to spinal cord compression should have additional assessment. Lytic bone disease is often diffuse in MM and may be confused with benign osteoporosis. In patients without radiologically detectable lytic lesions, but with a reasonable suspicion of myeloma requiring therapy, the majority of the panel recommends the use of an additional imaging technique (such as MRI, if available) of the spine in order to examine the risk of bone disease. MRI and radiographs are not always able to differentiate between treated bone marrow lesions and viable neoplastic tumors. 18F-fluorodeoxyglucose is taken up by metabolically active cells which can then be imaged using positron emission tomography (PET). High uptake by tumor cells is visible upon PET imaging as they have increased metabolic rates. While PET should not be used as a routine tool, it has advantages of being able to detect diffuse bone marrow involvement and extramedullary manifestations of MM that are often missed by MRI [188]. The use of bone biomarkers and various imaging modalities are being further evaluated to help define and diagnose bone disease in myeloma and may prove valuable in the future [189–193].

recommendations. The panel does not currently recommend the use of bone biomarkers either in SREs risk prediction or in optimization of BP therapy except as a part of a clinical trial (grade B). Plain radiographs remain the standard for evaluating bone disease; however, MRI can also be a valuable tool (grade C). In the absence of lytic lesions on radiographs, use of an additional imaging technique (e.g. MRI of the spine or whole body, if available) should be considered to examine the risk of bone complications (grade D).

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