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Clinical Practice Guidelines

Treatment of Multiple Myeloma-Related Bone Disease: Recommendations from the Bone Working Group of the International Myeloma Working Group (IMWG)

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Abstract

The IMWG updated the clinical practice recommendations for the management of multiple myeloma (MM)-related bone disease (MBD). Zoledronic acid (ZA) is the preferred bone targeted agent for newly-diagnosed MM (NDMM) patients with or without MBD. Once patients achieve VGPR or better, the treating physician may consider decreasing frequency or discontinuing ZA, if the patient has received one year of monthly ZA. Denosumab can be also considered for the treatment of MBD, particularly in patients with renal impairment. Denosumab may prolong PFS among NDMM patients with MBD, who are eligible for autologous transplantation. Denosumab discontinuation is challenging due to rebound phenomenon. Cement augmentation is effective for painful vertebral compression fractures. Radiotherapy is recommended for uncontrolled pain, impeding or symptomatic spinal cord compression or pathological fractures. Surgery should be used for the prevention and restoration of long-bone pathological fractures, vertebral column instability and SCC with bone fragments within the spinal route.

Key words: multiple myeloma, bone disease, recommendations, zoledronic acid, denosumab

Introduction

Multiple myeloma (MM) is a plasma cell dyscrasia with a high likelihood of development of bone disease (MBD); as a result, up to 80% of newly diagnosed MM (NDMM) patients present with osteolytic lesions.[1] These patients are at high risk for skeletal-related events (SREs) including pathological fractures, spinal cord compression and need for surgical or radiotherapeutic intervention.[2] SREs add significantly to the disease burden both in terms of survival and quality of life as well as public health costs.[2,3]

Differently from the past, conventional skeletal survey is no longer recommended for assessment of MBD due to the low sensitivity which ultimately results in failure to detect up to 25% of lytic lesions found at whole-body low-dose computed tomography (WBLDCT).[4,5] Therefore, WBLDCT constitutes the current standard for the diagnosis of MBD.[4,6] Positron emission tomography/computed tomography (PET/CT) and whole-body magnetic resonance imaging (WBMRI) are valuable imaging modalities as well.[6-8] PET/CT remains to-date the gold standard for the follow-up of MBD and assessment of metabolic response to therapy, including detection of residual disease after treatment.[7,9,10]

The pathophysiology of MBD has been well studied and results from MM cell interactions with bone cells including osteocytes, osteoblasts and osteoclasts.[11] MM-induced osteocyte apoptosis leads to a favorable niche for myeloma cell homing, while osteocytes produce soluble factors including receptor activator of nuclear factor (NF)-κB (RANK) ligand (RANKL), sclerostin and dickkopf-1, that promote osteoclast activity and impair osteoblast maturation, resulting in bone loss.[11,12] Suppressed osteoblast activity is mainly mediated by suppression of the Wingless-type (Wnt) and β-catenin pathway.[11] MM cells and osteocytes secrete Wnt antagonists such as sclerostin and dickkopf-1.[13,14] Increased osteoclast activity is driven by the activation of the RANK/RANKL signaling system.[15] Additional intracellular and intercellular signaling pathways participate in the complex pathogenesis of MBD,[11] including transforming growth factor-beta signaling[16,17]; the knowledge of these mechanism have led to the development of novel agents evaluated in clinical trials.[18,19]

Traditionally, bisphosphonates have been the gold standard for MBD prevention and treatment.[20] However, enhanced understanding of the underlying pathophysiological mechanisms has led to the clinical development of other targeted agents, including denosumab, a humanized monoclonal antibody directed against RANKL. Therefore, the International Myeloma Working Group aimed to review all currently available evidence and update previous recommendations for the management of MBD.[20,21]

Search strategy, selection criteria and methodology

An interdisciplinary panel of clinical experts on MM and MBD reviewed available evidence published in randomized clinical studies, meta-analyses, systematic reviews of published clinical studies, observational studies, and case reports through May 2020 and developed these recommendations on behalf of the IMWG. Expert panel consensus was implemented to propose additional recommendations when published clinical data were not considered as sufficient to draw firm conclusions. Levels of evidence and grades of recommendations were assigned using established criteria in line with the Grading of Recommendations Assessment Development and Evaluation (GRADE) system and in accordance to the previously published recommendations from the IMWG (Table 1).[20] The initial draft was circulated to each panel member for critical evaluation and to provide feedback on the levels of evidence and grading of recommendations. The manuscript subsequently underwent three rounds of revision between the panel members and final consensus was reached by all authors.

1. Bone-targeted agents

1A. Bisphosphonates

Bisphosphonates are pyrophosphate analogues which bind to exposed areas of hydroxyapatite crystals during the bone remodeling process. Osteoclasts endocytose bisphosphonates, which are potent inhibitors of the intracellular farnesyl pyrophosphate synthase, leading to osteoclast apoptosis and prevention of bone loss.[22]

Indications for treatment

Recommendations

Bisphosphonates (zoledronic acid, ZA or pamidronate) should be administered in all patients with active MM regardless of the presence (grade A) or absence (grade B for ZA only) of MBD on imaging studies. ZA is also indicated for the treatment of MM-related hypercalcemia and it is superior to pamidronate in this setting (grade B). In patients with smoldering MM (SMM) or those with a monoclonal gammopathy of undetermined significance (MGUS) or solitary plasmacytoma, bisphosphonates are recommended only if there is coexistence of osteoporosis; MGUS and SMM patients should be monitored and treated according to osteoporosis guidelines (grade C). For these patient groups, dual-energy x-ray absorptiometry (DXA) scan along with highly sensitive imaging modalities including WBLDCT, WBMRI or PET/CT should be used, as appropriate,[6] in order to both exclude the presence of active MM disease and evaluate bone health (grade D; panel consensus). Treatment of solitary plasmacytoma includes local radiotherapy; if radiotherapy fails and patient has to be treated as active myeloma then bisphosphonates have to be administered according to myeloma

recommendations (grade D; panel consensus). Patients diagnosed with high-risk SMM, SMM with one focal lesion in MRI or PET/CT (but without osteolysis in the CT part of PET/CT) and equivocal findings in WBLDCT and/or MRI (i.e. one lytic lesion smaller than 5mm in WBLDCT or two small focal lesions in MRI) may be considered for bisphosphonate treatment at a dosing schedule similar to patients with symptomatic MM (grade D; panel consensus).

Evidence

A network meta-analysis incorporating data from 24 randomized controlled trials (n=7,293 patients) demonstrated the favorable effect of bisphosphonates compared with placebo or no treatment in terms of preventing SREs and reducing bone pain indices.[23] Evaluation of bone pain should be interpreted with caution due to the high heterogeneity in assessment scales and blinding status among the included studies.[23] Notably, the randomized Medical Research Council Myeloma IX (MRC-IX) study (Table 2) showed that ZA administration reduced SRE incidence in MM patients without MBD at baseline.[24] However, it should be noted that in MRC-IX, MBD assessment was performed using only conventional radiography; therefore, a degree of patient misclassification cannot be ruled out.

Hypercalcemia in patients with MM is primarily attributed to underlying osteolytic disease.[25] A pooled analysis of two randomized trials including data from 275 patients with cancer has shown that ZA is superior to pamidronate in the reversal of hypercalcemia of malignancy.[26] Prompt initiation of anti-myeloma treatment including high dose of dexamethasone is also important for reducing serum calcium levels.[25]

Importantly, it has been shown that bone microarchitectural changes are evident even at the early stages of myelomatogenesis[27] and that patients with MGUS have an increased risk of fracture compared with age- and gender-matched controls, irrespective of progression to symptomatic MM.[28] Both ZA administered at 4mg intravenously (iv) every 6 months for 3 doses and alendronate administered at 70mg weekly orally (po) increased bone mineral density (BMD) indices in patients with MGUS and osteoporosis.[29] In patients with SMM, monthly iv treatment with both ZA (4mg) and pamidronate (60-90mg) for one year significantly reduced the occurrence of SREs at the time of progression to symptomatic MM compared with no intervention with low risk of development of osteonecrosis of the jaw (ONJ) in the respective studies.[30] However, no progression-free survival (PFS) advantage has been demonstrated with bisphosphonate monotherapy.[30-32] Therefore, the presence of osteoporosis should guide treatment with bisphosphonates in the absence of symptomatic MM disease. High-risk patients with SMM should be ideally treated in the context of a clinical trial.

Bisphosphonate choice, route of administration and dosing schedule

Recommendations

Among patients with symptomatic MM, iv ZA administered at 4 mg every 3-4 weeks over 15 minutes infusion and pamidronate administered at 30 or 90 mg, every 3-4 weeks, over 45 minutes or two hours, respectively, are recommended for SRE prevention (grade A). Dose adjustments for bisphosphonates are essential in case of renal impairment both at diagnosis and during treatment (discussed in detail in the section of "*Management of AEs-Evidence*").

Apart of its more convenient administration mode, ZA may be preferred over pamidronate due to a significant reduction in the mortality rate (grade B). ZA is preferred over clodronate due to its superiority in reducing SRE incidence and for improving survival especially in NDMM patients with MBD at diagnosis (grade A). Compared with placebo or no treatment, only ZA has shown both a PFS and overall survival (OS) benefit (grade A).

Pamidronate 90 mg administered every month is not superior to 30 mg for SRE prevention (grade B).

Outpatient iv bisphosphonate administration is preferred (grade A). For patients unable to receive hospital-based outpatient care, in-home nursing-assisted iv infusion may be considered as an alternative option; in such cases, ZA is preferred over pamidronate due to shorter infusion time (grade D).

Evidence

In the previously mentioned network meta-analysis, the approved bisphosphonates (ZA, pamidronate) showed a significant reduction in SRE incidence compared with control (placebo or no treatment).[23] However, only ZA administration demonstrated a PFS (HR=0.70; 95% CI: 0.52-0.95) and OS (HR=0.57; 95% CI: 0.43-0.75) benefit compared with control.[23] Furthermore, ZA is not inferior to pamidronate for preventing SREs (incidence reduction and delaying time to first SRE) and reducing bone pain.[33] Interestingly, in a record-based study (not-included in the meta-analysis) of 1,018 U.S. Veterans diagnosed with MM, ZA reduced the risk of death from any cause by 22% and decreased SRE incidence by 25% compared to pamidronate.[34] However, a higher proportion of patients developed ONJ in the ZA (2.6%) versus pamidronate (0.8%) group.[34]

ZA is superior to clodronate at reducing SREs in NDMM patients receiving upfront anti-myeloma treatment (27% versus 35%, p=0.004).[24] This favorable effect was evident, irrespective of the presence of MBD on conventional radiography at diagnosis or the administration of maintenance treatment with thalidomide.[24,35] In the MRC-IX trial, ZA also resulted in a significant reduction of mortality (by 16%) and improvement in PFS (by 12%) compared with clodronate.[36] We have to stress here that the difference in mortality was mainly due to the reduction of infections in the ZA arm. In subsequent subgroup analyses, the OS

benefit was more pronounced among MM patients with evidence of MBD at diagnosis.[35] The anti-myeloma activity of ZA may be partially attributable to either a direct effect by inhibiting protein prenylation, or an indirect effect by reducing the expression of bone marrow stromal cell-associated adhesion molecules, with both effects ultimately leading to myeloma cell apoptosis.[37]

Regarding pamidronate, a randomized, double-blind trial including 504 NDMM patients showed that monthly pamidronate administration at 30mg was equivalent to 90mg on physical function and median time to first SRE. Retrospectively, a trend towards reduced ONJ and kidney injury risks with pamidronate 30mg compared to 90mg was reported.[38]

Treatment adherence is a prerequisite for positive outcomes; thus, patient education is considered of outmost importance. Administration of iv bisphosphonates can be performed during a scheduled patient visit. The shorter infusion time of ZA renders it more convenient versus pamidronate for both patients and hospital staff.[39] Bisphosphonates may also be infused under nursing surveillance at home.[39] Clodronate remains an option outside the US in cases of inability for in-hospital or in-home iv bisphosphonate administration.[40]

Duration of treatment with bisphosphonates

Recommendations

ZA should be administered monthly, at least for 12 months (grade B). If after 12 months, response is VGPR or better the treating physician may consider to decrease the dosing to every 3 months or based on osteoporosis recommendations (every 6 months or yearly) or even to stop ZA. The decision to stop ZA in this setting should take into consideration an individualized evaluation of fracture risk based on gender, age, nationality, body mass index, history of previous fracture, smoking and alcohol drinking status, bone mineral density, systemic disease (other than MM) associated with secondary osteoporosis, daily and cumulative glucocorticoid dose, which is frequent in continuous anti-myeloma regimens (panel consensus).[41,42] If after 12 months, response is less than VGPR, ZA has to be continued monthly until the response is VGPR or better. Thereafter the treatment paradigm as described above can be applied (grade D, panel consensus).

Pamidronate should be administered in MM patients with active disease and may be continued at the physician's discretion taking into consideration patient- and disease-related factors, as aforementioned (grade D, panel consensus).

If discontinued, ZA/pamidronate should be reinitiated at the time of biochemical relapse because this reduces the risk of new bone event at clinical relapse (grade B).

Evidence

In the MRC-IX trial, patients receiving ZA therapy for two years or more showed improved OS compared with clodronate both from time of randomization and first disease progression.[35] Extending ZA administration from two to four years did not result in an OS benefit in another study including 170 NDMM patients.[43] SRE incidence rate was lower in the 4-year group; however no data on quality of MM responses were available.[43]

The introduction of novel quadruplet combinations, including an anti-CD38 monoclonal antibody, a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD) in the front-line treatment of NDMM patients, increase the depth of response; therefore, the necessity of continuous treatment with bisphosphonates in these patients for more than one year is questionable. Consolidation with bortezomib-based regimens following autologous transplantation has shown a favorable effect in bone metabolism and a very low SRE incidence in the absence of bisphosphonate co-administration in two prospective studies.[44,45] Importantly, more than half of the patients in the included studies had achieved complete response (CR) or better at the end of consolidation treatment.[44,45] In a retrospective analysis among transplant eligible patients recruited in the MRC-IX study (n=1,111), ZA retained its superiority in terms of SRE prevention only in the subset of patients achieving VGPR or less, on day 100 post-transplant (p=0.048). Interestingly, the OS benefit of ZA over clodronate was evident only among patients with post-transplant PR (p=0.009), but not among those in CR or VGPR.[46]

Studies have evaluated if reductions in bisphosphonate treatment intensity reduce long-term adverse events (AEs) such as ONJ, while retaining efficacy. A subgroup analysis of a randomized clinical trial incorporating data from 278 MM patients receiving ZA, either once monthly or every 3 months, for two years, indicated a similar probability of developing at least one SRE within the 2-year follow-up period.[47] Furthermore, a model based on levels of the urinary N-telopeptide of type 1 collagen (uNTX, a bone resorption biomarker) was implemented in the Z-MARK study, which evaluated dynamic adaptation of a ZA administration schedule according to biomarker levels measured every 3 months.[48] ZA was given monthly if uNTX ≥50 nmol/mmol creatinine and every 3 months if uNTX levels were < 50 nmol/mmol creatinine. This approach resulted in low SRE rates during the first (5.8%) and second (4.9%) years on study and a 2-year ONJ incidence rate of 3.3%.[48] Reduced uNTX levels are associated with fewer SREs among MM patients in remission who have discontinued therapy with ZA/pamidronate, suggesting the potential for less frequent dosing during remission.[49] The 3-month interval of ZA administration in responding patients has also been suggested by the European Myeloma Network (EMN) and other organizations for the management of MBD during the COVID-19 period.[50]

Regarding pamidronate, a trend towards improved OS compared with placebo has been demonstrated at first relapse.[51] Post-transplant thalidomide maintenance with pamidronate did not result in a significant reduction in SRE occurrence or an OS improvement compared with thalidomide monotherapy.[52] In both treatment groups, VGPR or better rates were above 56%.[52]

There has been also preliminary evidence showing that patients with MM, in sustained remission for more than two years, experience a gradual increase in lumbar spine BMD in the absence of bisphosphonate administration.[53]

In a Spanish study, patients, who were at biochemical relapse, were randomized to ZA versus no bisphosphonate. The patients had been formerly treated with bisphosphonate but this had been stopped in first remission.[54] ZA did not prolong time to demanding disease or survival but reduced the risk of new bone events at time of start of new anti-myeloma treatment.

Management of AEs

Recommendations

Calcium and vitamin D supplementation should be administered to all patients receiving bisphosphonates (grade A), following normalization of serum calcium levels in case of hypercalcemia. Creatinine clearance (CrCl), serum electrolytes and urinary albumin (only for pamidronate) should be monitored monthly and dose adjustments should be made accordingly (grade A). A comprehensive dental examination and any necessary invasive treatment should be performed before bisphosphonate initiation (grade C). Bisphosphonates should be discontinued in cases of ONJ unless continued treatment is highly needed, e.g. progression of lytic bone disease or recurrent hypercalcemia. If clinically acceptable, bisphosphonates should be temporarily paused before and after any dental extraction or invasive oral procedures. Periprocedural antibiotic prophylaxis should be considered (panel consensus). Hereafter, bisphosphonate may be re-initiated based on individualized risk/benefit considerations (grade D; panel consensus). Patient education is essential for adherence to dental hygiene and supplement intake, as well as for early recognition and reporting of AEs (grade D; panel consensus).

Evidence

Calcium and vitamin D supplementation are important for preventing severe hypocalcemia, not at least in MM patients where vitamin D deficiency is common.[55] Vitamin D is essential for calcium uptake and normal bone remodeling. The Institute of Medicine (IOM) has issued recommendations for calcium and vitamin D daily intake in older adults. For women older than 50 years, the IOM recommended 1200 mg/day of calcium. The IOM recommended 1000

mg/day of calcium for men 51-70 years of age and 1200 mg/day for men over 70. For both sexes, the recommended upper level was 2000 mg/day. For both women and men, the recommended daily dietary allowance of vitamin D was 600 IU from age 51-70 and 800 IU for after age 70, with a recommended maximum of 4000 IU.[56] Patients with renal impairment receiving calcium supplements need close monitoring.

Routine evaluation of renal function is important because bisphosphonates may induce acute renal damage.[33,57] ZA and clodronate should be administered at reduced doses and pamidronate with extended duration (i.e. 4h) in patients with CrCl between 30 and 60ml/min. ZA and pamidronate should be administered only when CrCl is above 30ml/min; for clodronate the cut-off value of CrCl is 12ml/min.[58] Re-initiation of bisphosphonates should be considered upon restoration of serum creatinine levels to within 10% of baseline values. Albuminuria should be monitored during pamidronate administration due to glomerular toxicity of pamidronate.[39]

ONJ is an uncommon but debilitating AE that has been primarily associated (among bisphosphonates) with prolonged administration of ZA.[59-62] However, a meta-analysis did not show an excessive risk of ONJ with ZA compared with other bisphosphonates.[23] Interestingly, the majority of ONJ cases heal; therefore, bone-targeted treatment can be restarted, especially among MM patients who developed ONJ after a surgical intervention in the oral cavity.[61] Preventive measures are effective in reducing the incidence of ONJ.[63,64] Although the documented clinical evidence is scarce, a 6-month periprocedural (3 months before and 3 months after) drug holiday is suggested for elective dental procedures based on bisphosphonate pharmacokinetics and bone physiology, especially in patients responding to anti-myeloma therapy.[65] Taking into consideration the long-term exposure to corticosteroids and the immunosuppressive state due to MM and anti-myeloma treatments, antibiotic prophylaxis such as amoxicilline-clavulanate 1 day before until 3 days after the invasive dental procedure should be considered.[64] The risk for infection should be evaluated based on dental hygiene, patient comorbidities and MM disease status. Depending on the local clinical practice and the individualized risk assessment, penicillin with or without a beta-lactamase inhibitor and metronidazole are possible options. A multidisciplinary approach is important.[66]

1B. Denosumab

Denosumab is an IgG2 fully human and highly specific monoclonal antibody against RANKL. Denosumab imitates the physiological effect of osteoprotegerin by inhibiting RANKL interaction with RANK, ultimately decreasing bone resorption.[1]

Indications for treatment

Recommendations

Denosumab is recommended for the treatment of NDMM patients (grade A) and patients with relapsed/refractory MM (RRMM) (grade B) with evidence of MBD. Denosumab is equivalent to ZA in terms of delaying the time to first SRE following MM diagnosis (grade A). Denosumab may prolong PFS among NDMM patients with MBD who are eligible to receive an autologous stem cell transplant (ASCT) (grade B). Denosumab may be preferred over ZA in patients with MM and renal dysfunction (grade B). Denosumab may be considered for patients with CrCl less than 30 ml/min under close monitoring (grade D, panel consensus). Denosumab can be also administered in patients with hypercalcemia related to myeloma, especially in those who are refractory to ZA administration (grade B).

In patients with SMM or those with MGUS or solitary plasmacytoma, denosumab is recommended only if there is coexistence of osteoporosis, according to osteoporosis guidelines (60 mg, sc, every 6 months) (grade D, panel consensus).

Evidence

To date, the largest study evaluating the comparative efficacy and safety of denosumab to ZA among MM patients is the 20090482 phase 3 clinical trial (Table 2).[67] This multicenter, double-dummy and double-blind, randomized (1:1) controlled trial included 1,718 NDMM patients. The study met its primary endpoint of non-inferiority of denosumab compared with ZA in delaying time to first SRE (HR=0.98; 95% CI :0.85-1.14, p=0.010) following a median time on study of 17.3 months for denosumab and 17.6 months for ZA patient group.[67] This study confirmed the results of a previous phase 3 trial that had also shown the non-inferiority of denosumab compared with ZA in preventing or delaying time to first SRE in a subset of NDMM and relapsed-refractory MM (RRMM) patients (n=180, HR=1.03; p=0.89).[68] As the majority of first on-study SREs in both treatment groups was reported in the first 6 months in the 20090482 trial, a landmark analysis at 15 months was performed in order to assure adequate exposure to bone-targeted agents. This *post-hoc* analysis showed that denosumab significantly prolonged the time to first SRE compared with ZA (HR=0.66; 95% CI: 0.44-0.98, p=0.039).[67] Furthermore, when denosumab is administered with standard first-line treatment for NDMM patients, it improves PFS by 10.7 months compared with ZA (HR=0.82; 95% CI: 0.68-0.99, p=0.036). In subsequent subgroup analyses the benefit of denosumab in terms of

PFS was particularly evident among patients with an intention to undergo ASCT (HR=0.65; 95% CI: 0.49-0.85, p=0.002); importantly, no significant differences between the two treatment groups were reported regarding patient and disease characteristics.[69,70] No difference in OS between the two ZA and denosumab has been suggested so far.

Renal toxicity was more common among patients receiving ZA (17%) than those receiving denosumab (10%). Among patients with renal insufficiency (CrCl 30-60 ml/min), renal AEs were doubled in the group of ZA (26%) compared with the denosumab group (13%).[67] Patients with CrCl less than 30 ml/min were not included in the 20090482 trial; thus for this patient group we may only extrapolate data based on osteoporosis studies showing the feasibility of denosumab administration regardless of kidney function.[71,72]

Denosumab can be used for the treatment of hypercalcemia of malignancy that is refractory to bisphosphonates based on the results of a single arm study including 33 patients with solid and hematological cancer.[73,74] Interestingly, a pooled analysis of two phase 3 clinical trials has shown that denosumab is superior to ZA in preventing or delaying the emergence of hypercalcemia of malignancy among patients with advanced solid tumors and MM.[75]

Route of administration, dosing schedule and duration of treatment with denosumab

Recommendations

Denosumab should be administered as a subcutaneous injection of 120mg at monthly intervals (grade A). Subcutaneous injection at home may avoid hospital visits during the COVID-19 pandemic and makes denosumab administration easier compared to bisphosphonates for this period. Denosumab should be given continuously until unacceptable toxicity (grade A). Dosing de-intensification or drug holiday or discontinuation might be considered only after 24 months of treatment and if patient has responded to to anti-MM treatment defined as VGPR or better (grade D, panel consensus). A tailored evaluation based also on patient characteristics, comorbidities and steroid use should guide treatment decisions, as previously discussed with bisphosphonates. Until further data is available on myeloma patients, a single dose of iv bisphosphonate (i.e. ZA) is recommended at least 6 months after the last denosumab dose in order to prevent a potential rebound effect; similarly, denosumab administration every 6 months may be also taken into consideration (grade D, panel consensus)

Evidence

In the phase 3 20090482 clinical trial, denosumab was administered at 120mg subcutaneously once every month continuously.[67] Denosumab injection can be given during a routine clinic visit. During the COVID-19 pandemic, sc administration makes home delivery of denosumab easier compared to iv bisphosphonates.[50] Weekly administration for one month

and then switching to monthly injections may be considered for patients with ZA-refractory hypercalcemia due to MM.[74]

Discontinuation of denosumab therapy is not supported by clinical data in myeloma. However, osteoporosis literature data demonstrate that denosumab discontinuation is followed by a rebound osteoclastogenesis, 6-12 months after denosumab discontinuation, with rapid reduction of BMD and an increased risk for vertebral fractures,[76,77] even in patients who had been previously treated with bisphosphonates.[78] The European Calcified Tissue Society has recommended that denosumab discontinuation be followed by bisphosphonate administration in order to reduce the rebound phenomenon.[76] In myeloma patients, it is less certain that the re-bound phenomenon will occur, as anti-myeloma agents (PIs, IMiDs, daratumumab) have anti-osteoclast activity and counteract bone resorption.[79,80] Nevertheless, taking into consideration the lack of data on the effect and management of treatment discontinuation with denosumab among myeloma patients, extrapolating the evidence from osteoporosis studies,[1,76] we suggest that a single dose of ZA, iv., at least 6 months post-denosumab discontinuation has to be given if a physician wants to discontinue denosumab. Another alternative would be the administration of denosumab every 6 months. Data on this issue is highly anticipated.

Management of AEs

Recommendations

Calcium and vitamin D supplementation is recommended for all patients receiving denosumab, especially those with renal impairment (grade A), following normalization of serum calcium levels in case of hypercalcemia. Serum calcium, vitamin D, phosphate and magnesium should be evaluated on a regular basis to evaluate the need for additional supplementation (grade C, panel consensus). Oral health should be evaluated at baseline and assessed during treatment with denosumab (grade C; panel consensus). Denosumab should be discontinued 30 days before invasive dental or oral procedures until healing occurs, when they can be re-initiated (grade D; panel consensus).

Evidence

In the 20090482 trial, hypocalcemia was more frequent with denosumab (17%) than ZA (12%); thus preventive measures should be taken.[67] CrCl and serum alkaline phosphatase may predict for hypocalcemia risk.[81] See also respective paragraph for calcium and vitamin D daily uptake in bisphosphonate adverse events session.

ONJ incidence did not differ between the two groups (4% versus 3%, p=0.147) and preventive dental measures are considered essential.[67,82]

2. Other approaches: cement augmentation, radiotherapy and surgery

Recommendations

A thorough evaluation of bone health based on medical history, clinical examination, laboratory analyses and imaging in order to estimate the risk for SRE is recommended for all MM patients (panel consensus). NDMM patients at high risk for developing SREs should be considered for an early intervention in addition to the administration of bone-targeted agents (panel consensus). Balloon kyphoplasty (BKP) (grade A) and vertebroplasty (grade C) are recommended for patients with painful vertebral compression fractures. Radiotherapy should be considered for uncontrolled pain due to impeding or symptomatic spinal cord compression (SCC) and due to pathological fractures (grade C). Surgery should be considered for prevention and restoration of long-bone pathological fractures, vertebral column instability and SCC with bone fragments within the spinal route (grade C). Adjuvant radiotherapy should be considered for long-bone pathological fractures due to underlying plasmacytoma, especially for patients with minimal or no response to systemic anti-myeloma treatment (panel consensus).

Evidence

Both prospective[67] and retrospective data[83] have shown that the majority of SREs occur early relative to the time of initial diagnosis or relapse. Among the first on-study SREs in the 20090482 study, 60% and 81% were reported in the first 3 and 6 months, respectively.[67] Uncontrolled pain is a devastating symptom for MM patients with vertebral fractures. Therefore, immediate effects of bone-targeted agents for SRE prevention are rather questionable and early intervention with other approaches may be necessary. MBD burden, presence of osteoporosis, progressive clinical deterioration, previous history of any SREs, therapeutic treatment approach and treatment duration should be taken into consideration to permit characterization of the high-risk population.[83]

The value of balloon kyphoplasty has been shown in a randomized study including 134 patients with painful vertebral body compression fractures due to bone metastases or MM.[84] In the international Cancer Patient Fracture Evaluation (CAFE) study, 70 patients were randomized to receive kyphoplasty along with non-surgical interventions and 64 received only non-surgical management. BKP was associated with clinically meaningful improvement in physical functioning, back pain, quality of life, and ability to perform daily activities compared with non-surgical management. It has to be noted that less than 10% of the patients underwent radiotherapy in both treatment groups. Importantly, these benefits persisted throughout the 12-month study period.[84] Furthermore, several non-randomized studies have shown that kyphoplasty and vertebroplasty are effective in reducing pain scores and restoring functionality

in patients with MM.[85-87] IMWG has recently produced guidelines for the use of cement augmentation in MM patients.[88]

Low-dose radiation therapy (up to 30 Gy) can be also used as palliative treatment for uncontrolled pain, for impending pathologic fracture, or impending SCC (urgent condition). Radiotherapy is highly effective in pain relief that can be achieved in up to 90% of the patients.[89,90] 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.[91] No difference in analgesic and recalcification effect between the uni- and multi-fractioned radiotherapy regimen was also shown in another randomized study including 101 patients with MM.[89] Initial radiotherapy may be followed by cement augmentation to ensure stabilization of the spine on an individualized basis.[88] However, treatment sequence does not seem to impact pain improvement.[91]

Orthopedic consultation should be sought for impending or actual long-bone fractures, bony compression of the spinal cord, or vertebral column instability.[88] Orthopedic surgical treatment of MBD is effective in the improvement of symptoms and quality of life.[92] However, these patients have a high risk of perioperative surgical and medical complications that may reach 74%, taking into consideration that the majority of the patients are newly diagnosed and in need of immediate initiation of systemic treatment.[93] In this context, multidisciplinary management is considered essential.[92,93] Although a randomized trial has showed the superiority of direct decompressive surgery followed by radiotherapy compared to radiotherapy alone among patients with spinal cord compression due to metastatic solid cancer, no pertinent randomized data on patients with MM are available.[94] Post-operative radiotherapy should be considered especially for long-bone fractures in order to achieve local disease control and prevent implant failure.[95] This is particularly important for patients with minimal or no response to systemic anti-myeloma treatment.

An algorithmic approach should guide the decision to proceed with kyphoplasty/vertebroplasty[87,88], radiotherapy[89,90] or surgery[92] especially in patients with neurological symptoms (Figure 1).

Conclusions

Bisphosphonates or denosumab should be considered as the standard of care for treating MBD (Table 3). The decision to choose one bone-targeted agent over another should include consideration of multiple factors including cost, convenience, patient preference, and toxicity profile. Economic models have shown that denosumab is a cost-effective treatment both in the USA[96] and Europe[97] over ZA. However, these studies have the limitation that the costs were estimated from multiple sources, which varied by patient population, country, and other

parameters, while PFS and overall survival were extrapolated beyond the follow-up of the primary analysis of the phase 3 study comparing denosumab with ZA, using fitted parametric curves. We suggest that until further data is available, ZA should be preferred in patients who do not have imaging findings for MBD, whereas denosumab should be preferred in patients with renal impairment.

Preventive measures to avoid renal impairment, hypocalcemia and ONJ are considered essential for all bone-targeted agents. Cement augmentation, radiotherapy and surgery should be implemented in specific situations such as cord compression, pain control and pathological fractures of weight bearing bones. Ongoing clinical trials are investigating the role of denosumab in patients with CrCl <30 ml/min (NCT#02833610). Other novel bone anabolics are also currently under investigation.

Panel

Search strategy and selection criteria

An interdisciplinary panel of clinical experts on MM and MBD reviewed available evidence published in randomized clinical studies, meta-analyses, systematic reviews of published clinical studies, observational studies, and case reports. The Medline, Embase and Cochrane bibliographic databases, along with abstract lists from major hematology-oncology conferences including ASH, ASCO, EHA, ESMO were searched from conception through 31st May 2020. Potentially eligible studies written in English, French, German or Spanish were sought with a combination of the following search terms: “multiple myeloma”, “myeloma”, “bone”, “osteolytic”, “osteolyses”, “bisphosphonates”, “zoledronic acid”, “pamidronate”, “denosumab”, “RANKL”, “osteoclast”, “osteoblast”, “skeletal related event”, “cement augmentation”, “kyphoplasty”, “vertebroplasty”, “radiotherapy”, “orthopedic”. Expert panel consensus was implemented to propose additional recommendations when published clinical data were not considered as sufficient to draw firm conclusions. Levels of evidence and grades of recommendations were assigned using established criteria in line with the Grading of Recommendations Assessment Development and Evaluation (GRADE) system and in accordance to the previously published recommendations from the IMWG (Table 1). The initial draft was circulated to each panel member for critical evaluation and to provide feedback on the levels of evidence and grading of recommendations. The manuscript subsequently underwent three rounds of revision between the panel members and final consensus was reached by all authors.

Author contributions

Conception and design: ET, EZ, NR

Collection and assembly of data: ET, IN-S, NR

Data analysis and interpretation: All

First draft writing: ET, EZ, IN-S, NR

Manuscript writing: All authors; **Final approval:** All authors

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Tables

Table 1. Levels of evidence and Grades of recommendations

Level/Grade	Description
Level of evidence	
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 false-negative errors (low power)
III	Evidence obtained from well-designed, quasi-experimental studies such as nonrandomized controlled single-group, pre-post, cohort, time, or matched case-control series
IV	Evidence from well-designed, nonexperimental studies such as comparative and correlational descriptive and case studies
V	Evidence from case reports and clinical examples
Grade of recommendation	
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 the two largest randomized-controlled trials (MRC Myeloma IX and 20090482) evaluating bone-targeted agents in the treatment of MBD.[24,35,36,62,67,69]

	MRC Myeloma IX	20090482
Treatment drug	Zoledronic acid vs Clodronate	Denosumab vs Zoledronic acid
Treatment schedule	4 mg zoledronic acid iv every 3-4 weeks or 1600 mg oral clodronic acid daily	sc Denosumab 120 mg plus iv placebo or iv Zoledronic acid 4 mg plus sc placebo every 4 weeks
Population characteristics	NDMM patients with or without evidence of MBD	NDMM patients with evidence of MBD
Number of patients	981 vs 979	859 vs 859
Median time to first SRE (months)	NR	22.8 vs 24 (**$p_{non\text{-}inferiority}$=0.01**)
SRE incidence	27% vs 35% (**p=0.0004**)	43.8% vs 44.6%
PFS	HR=0.88; 95%CI: 0.80-0.98, **p=0.018**	HR=0.82; 95%CI: 0.68-0.99, **p=0.036**
OS	HR=0.84; 95%CI: 0.74-0.96, **p=0.012**	HR=0.90; 95%CI: 0.70–1.16; p=0.41
ONJ	3.7% vs 0.5%	4.1% vs 2.8%
Renal toxicity	5.2% vs 5.8%	10% vs 17.1%
Hypocalcemia	NR	17% vs 12%

Bold values denote statistical significance

MBD: myeloma-related bone disease; SRE: skeletal-related events; ONJ: osteonecrosis of the jaw; PFS: progression-free survival; OS: overall survival; NR: not reported; sc: subcutaneous; iv: intravenous; HR: hazard ratio; CI: confidence interval; NDMM: newly diagnosed multiple myeloma

Table 3. Summary of the updated recommendations for the treatment of MBD

Factor	Recommendation
Patient population	Newly diagnosed Myeloma (NDMM) Patients and Patients with Relapsed/Refractory Myeloma (RRMM)
Choice	1st option: **Zoledronic acid** (regardless of the presence of MBD on imaging for both NDMM and RRMM patients and also in patients at biochemical relapse) **Denosumab** (only in the presence of MBD on imaging – consider also for patients with renal impairment) 2nd option: **Pamidronate**
Administration	Zoledronic Acid, Pamidronate – iv Denosumab – sc
Duration / Frequency	**Zoledronic acid**: Monthly during initial therapy and in patients in less than VGPR; Once patients achieve VGPR or better, the treating physician may consider decreasing frequency of dosing to every 3 months or based on osteoporosis recommendations (every 6 months or yearly) or even to stop ZA, if patients have received monthly administration for at least 12 months . If discontinued, it should be reinitiated at the time of biochemical relapse, because this reduces the risk of new bone event at clinical relapse. **Denosumab**: continuously, monthly; If discontinued, a single dose of ZA should be given to prevent rebound phenomenon at least 6 months post last dose of denosumab; also consider giving denosumab every 6 months
Monitoring and Preventive measures	• CrCl, serum electrolytes (monthly) for ZA plus urinary albumin (monthly) for pamidronate; this is not needed for denosumab • Dental health (at baseline then at least annually or upon symptoms) for both BPs and denosumab • Calcium and Vitamin D3 supplementation is recommended for all patients for both BPs and denosumab • Patient education for early recognition and reporting of AEs for both BPs and denosumab

NDMM: newly diagnosed multiple myeloma; BPs: bisphosphonates; ZA: zoledronic acid; MBD: myeloma-related bone disease; sc: subcutaneous; iv: intravenous; VGPR: very good partial response; AE: adverse event

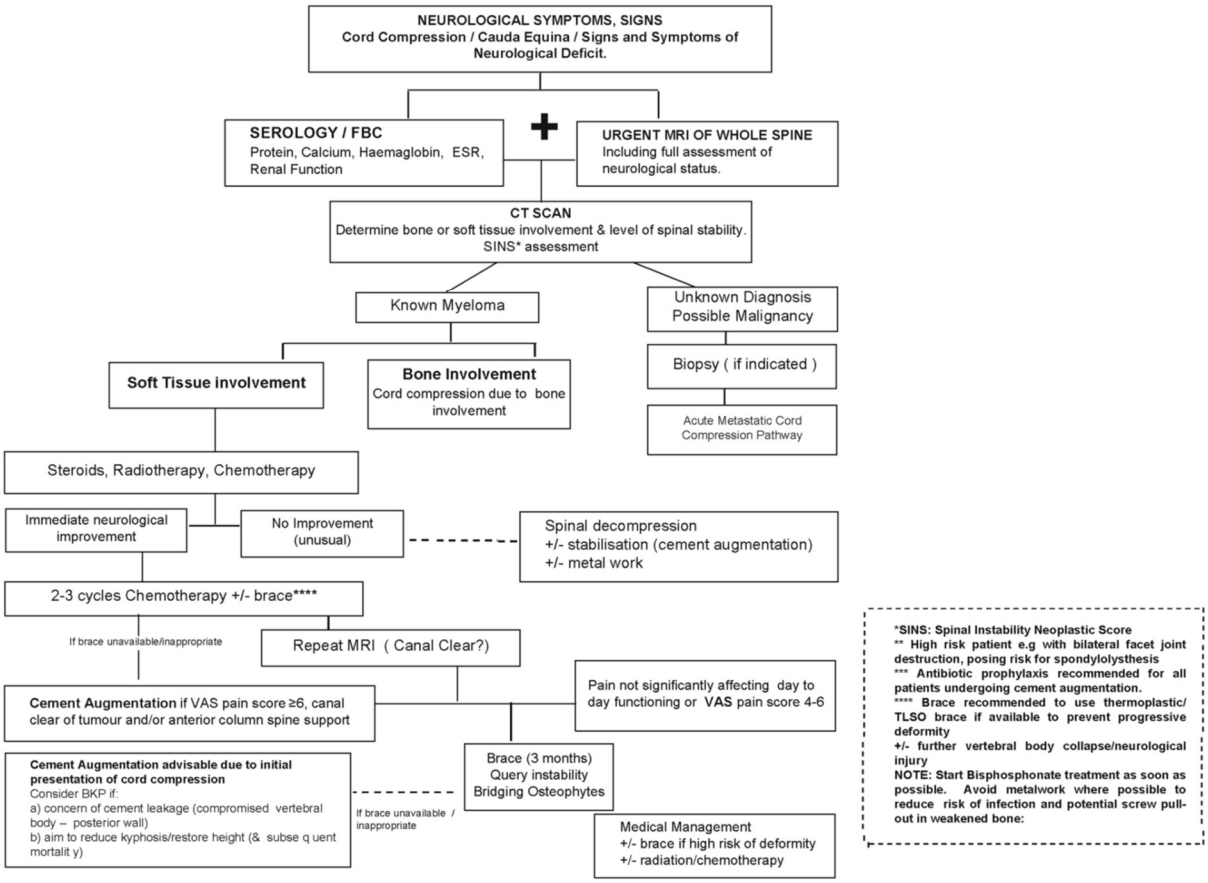

Figure 1. Algorithm for the use of cement augmentation, radiotherapy and surgery in vertebral complications due to myeloma.