Treatment of multiple myeloma-related bone disease: recommendations from the Bone Working Group of the International Myeloma Working Group

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In this Policy Review, the Bone Working Group of the International Myeloma Working Group updates its clinical practice recommendations for the management of multiple myeloma-related bone disease. After assessing the available literature and grading recommendations using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) method, experts from the working group recommend zoledronic acid as the preferred bone-targeted agent for patients with newly diagnosed multiple myeloma, with or without multiple myeloma-related bone disease. Once patients achieve a very good partial response or better, after receiving monthly zoledronic acid for at least 12 months, the treating physician can consider decreasing the frequency of or discontinuing zoledronic acid treatment. Denosumab can also be considered for the treatment of multiple myeloma-related bone disease, particularly in patients with renal impairment. Denosumab might prolong progression-free survival in patients with newly diagnosed multiple myeloma who have multiple myeloma-related bone disease and who are eligible for autologous stem-cell transplantation. Denosumab discontinuation is challenging due to the rebound effect. The Bone Working Group of the International Myeloma Working Group also found cement augmentation to be 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 spinal cord compression with bone fragments within the spinal route.

Introduction

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

Conventional skeletal survey is no longer recommended for multiple myeloma-related bone disease assessment due to low sensitivity, which results in a failure to detect up to 25% of lytic lesions when using whole-body low-dose CT. Therefore, whole-body, low-dose CT constitutes the current standard for the diagnosis of multiple myeloma-related bone disease.[3] PET-CT and whole-body MRI are also valuable imaging modalities for multiple myeloma-related bone disease assessment.[3,4] PET-CT remains the gold standard for the follow-up of multiple myeloma-related bone disease and assessment of metabolic response to therapy, including detection of residual disease after treatment.[4,5]

The pathophysiology of multiple myeloma-related bone disease has been well studied and has been shown to result from multiple myeloma cell interactions with bone cells, including osteocytes, osteoblasts, and osteoclasts.[6] Multiple myeloma-induced osteocyte apoptosis leads to a favourable niche for myeloma cell homing. Osteocytes also produce soluble factors, including receptor activator of NF-κB (RANK, also known as TNFRSF11A) ligand (RANKL, also known as TNFSF11), sclerostin, and Dickkopf-1, which promote osteoclast activity and impair osteoblast maturation, resulting in bone loss.[6,7] Suppressed osteoblast activity is mediated mainly by suppression of the Wnt and β-catenin pathway.[6] Multiple myeloma cells and osteocytes secrete Wnt antagonists, such as sclerostin and Dickkopf-1.[8,9] Increased osteoclast activity is driven by the activation of the RANK–RANKL signalling system.[10] Additional intracellular and intercellular signalling pathways participate in the complex pathogenesis of multiple myeloma-related bone disease and have led to the development of novel agents that have been evaluated in clinical trials.[6]

Traditionally, bisphosphonates have been the gold standard for multiple myeloma-related bone disease prevention and treatment.[11] However, an enhanced understanding of the underlying pathophysiological mechanisms of multiple myeloma-related bone disease has led to the clinical development of other targeted agents, such as denosumab, a humanised monoclonal antibody directed against RANKL. Therefore, the International Myeloma Working Group aimed to review all currently available evidence on multiple myeloma-related bone disease and update previous recommendations for its management.[11]

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See Online for appendix

Data collection

Search strategy and selection criteria

An interdisciplinary panel of clinical experts on multiple myeloma and multiple myeloma-related bone disease (which constitutes the authorship of this paper) reviewed available evidence published in randomised 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 haematology–oncology conferences including the American Society of Hematology, the American Society of Clinical Oncology, the European Hematology Association, and the European Society for Medical Oncology were searched from conception to May 31, 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", and "orthopedic".

Levels of evidence, grade recommendations, and consensus formation

Levels of evidence and grades of recommendations were assigned using established criteria in line with the Grading of Recommendations, Assessment, Development, and Evaluation (also known as GRADE) system and in accordance with the previously published recommendations from the International Myeloma Working Group[11] (appendix). 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. Expert panel consensus (at least 16 of 19 authors for each recommendation) was implemented to propose additional recommendations when published clinical data were not considered as sufficient to draw firm conclusions. The manuscript subsequently underwent three rounds of revision between the panel members and final consensus was reached by all authors.

Bisphosphonates

Bisphosphonates are pyrophosphate analogues that bind to exposed areas of hydroxyapatite crystals during the bone remodelling process. Osteoclasts endocytose bisphosphonates, which are potent inhibitors of the intracellular farnesyl pyrophosphate synthase, leading to osteoclast apoptosis and prevention of bone loss.[12]

Indications for treatment

Recommendations

Bisphosphonates (namely, zoledronic acid or pamidronic acid) should be administered to all patients with active multiple myeloma, regardless of the presence (grade A recommendation) or absence (grade B recommendation, for zoledronic acid only) of multiple myeloma-related bone disease on imaging studies. Zoledronic acid is also indicated for the treatment of multiple myeloma-related hypercalcaemia and is superior to pamidronic acid in this setting (grade B recommendation). For patients with smouldering multiple myeloma, monoclonal gammopathy of undetermined significance, or solitary plasmacytoma, bisphosphonates are recommended only if there is coexistence of osteoporosis; patients with monoclonal gammopathy of undetermined significance and smouldering multiple myeloma should be monitored and treated according to osteoporosis guidelines (grade C recommendation). For these patient groups, dual-energy x-ray absorptiometry scan should be used, along with highly sensitive imaging modalities including whole-body, low-dose CT, whole-body MRI, or PET-CT, as appropriate,[3] to exclude the presence of active multiple myeloma and evaluate bone health (grade D recommendation; panel consensus). Treatment of solitary plasmacytoma includes local radiotherapy; if radiotherapy fails and the patient has to be treated for active myeloma, then bisphosphonates have to be administered according to myeloma recommendations (grade D recommendation; panel consensus). Patients diagnosed with high-risk smouldering multiple myeloma, or smouldering multiple myeloma with one focal lesion in MRI or PET-CT (but without osteolysis in the CT part of the PET-CT scan) or with equivocal findings on whole-body, low-dose CT, whole-body MRI, or both (ie, one lytic lesion <5 mm in whole-body, low-dose CT or two small focal lesions on MRI) can be considered for bisphosphonate treatment. This treatment schedule should be given with a dosing schedule similar to that used for patients with symptomatic multiple myeloma (grade D recommendation; panel consensus).

Evidence

A network meta-analysis incorporating data from 24 randomised controlled trials (with a total of 7293 patients) showed the favourable effect of bisphosphonates compared with placebo or no treatment in preventing skeletal-related events and reducing bone pain indices.[13] Evaluation of bone pain should be interpreted with caution due to the high heterogeneity in the assessment scales used and blinding status of the different studies included.[13] Notably, the randomised Medical Research Council (MRC) Myeloma IX trial (table) showed that zoledronic acid performed better than clodronic acid in reducing the incidence of skeletal-related events in patients with multiple myeloma and for patients without multiple myeloma-related bone disease at baseline.[14] However, it should be noted that in MRC Myeloma IX, multiple myeloma-related bone disease assessment was done using only conventional radiography; therefore, a degree of undetected underlying osteolytic bone disease (and consequent patient misclassification) cannot be ruled out.

	MRC Myeloma IX	NCT01345019
Treatment drug	Zoledronic acid *vs* clodronic acid	Denosumab *vs* zoledronic acid
Treatment schedule	Zoledronic acid 4 mg intravenously every 3–4 weeks or clodronic acid 1600 mg orally daily	Denosumab 120 mg subcutaneously + placebo intravenously or zoledronic acid 4 mg intravenously + placebo subcutaneously every 4 weeks
Population characteristics	Patients with newly diagnosed multiple myeloma, with or without evidence of myeloma-related bone disease	Patients with newly diagnosed multiple myeloma, with myeloma-related bone disease
Number of patients	981 *vs* 979	859 *vs* 859
Median time to first skeletal-related event, months	NR	22·8 (95% CI 14·7–not estimable) *vs* 24·0 (16·5–33·3); $p_{non\text{-}inferiority}$=0·010
Incidence of skeletal-related events	27% *vs* 35% (p=0·0004)	44% *vs* 45%
Progression-free survival	HR 0·88, 95% CI 0·80–0·98; p=0·018	HR 0·82, 95% CI 0·68–0·99; p=0·036
Overall survival	HR 0·84, 95% CI 0·74–0·96; p=0·012	HR 0·90, 95% CI 0·70–1·16; p=0·41
Osteonecrosis of the jaw	4% *vs* <1%	4% *vs* 3%
Renal toxicity	6% *vs* 6%	10% *vs* 17%
Hypocalcaemia	NR	17% *vs* 12%

p values less than 0·05 are significant. HR=hazard ratio. MRC=Medical Research Council. NR=not reported.

Table: **Data from the MRC Myeloma IX and NCT01345019 trials evaluating bone-targeted agents in the treatment of myeloma-related bone disease**

Hypercalcaemia in patients with multiple myeloma is primarily attributed to underlying osteolytic disease.[15] A pooled analysis of data from two randomised trials that included 275 patients with cancer has shown that zoledronic acid is superior to pamidronic acid in the reversal of hypercalcaemia resulting from malignancy.[16] Prompt initiation of antimyeloma treatment, including high-dose dexamethasone, is also important to reduce serum calcium concentrations.[15]

Importantly, it has been shown that bone microarchitectural changes are evident even at the early stages of myelomatogenesis[17] and that patients with monoclonal gammopathy of undetermined significance have an increased risk of fracture compared with age-matched and sex-matched controls, irrespective of progression to symptomatic multiple myeloma.[18] Both zoledronic acid 4 mg administered intravenously every 6 months for a total of three doses and alendronic acid 70 mg administered weekly orally increased bone mineral density indices in patients with monoclonal gammopathy of undetermined significance and osteoporosis.[19] In patients with smouldering multiple myeloma, monthly intravenous treatment with both zoledronic acid 4 mg and pamidronic acid 60–90 mg for 1 year significantly reduced the occurrence of skeletal-related events at the time of progression to symptomatic multiple myeloma when compared with no intervention.[20] Both studies showed a low risk of development of osteonecrosis of the jaw. However, no progression-free survival advantage has been shown with bisphosphonate monotherapy.[20–22] Therefore, the presence of osteoporosis should guide treatment with bisphosphonates in the absence of symptomatic multiple myeloma disease. Patients with smouldering multiple myeloma and osteoporosis are at a high risk of bone fractures and should ideally be treated in the context of a clinical trial.

Bisphosphonate choice, route of administration, and dosing schedule

Recommendations

Among patients with symptomatic multiple myeloma, zoledronic acid 4 mg administered intravenously every 3–4 weeks over 15 min infusion, and pamidronic acid 30 mg or 90 mg administered every 3–4 weeks over 45 min (for 30 mg) or 2 h (for 90 mg) are recommended for skeletal-related event prevention (grade A recommendation). Dose adjustments for bisphosphonates are essential in case of renal impairment, both at diagnosis and during treatment.

In addition to its more convenient administration mode, zoledronic acid might be preferred to pamidronic acid due to a significant reduction in the mortality rate (grade B recommendation). Zoledronic acid is preferred to clodronic acid due to its superiority in reducing skeletal-related events and in improving survival, especially in patients with newly diagnosed multiple myeloma and multiple myeloma-related bone disease at diagnosis (grade A recommendation). Compared with placebo or no treatment, only zoledronic acid has shown both progression-free survival and overall survival benefits (grade A recommendation). Pamidronic acid 90 mg administered intravenously monthly is not superior to pamidronic acid 30 mg intravenously monthly for skeletal-related event prevention (grade B recommendation).

For outpatients, intravenous bisphosphonate administration is preferred over intravenous pamidronic acid or oral clodronic acid (grade A recommendation). For patients unable to receive hospital-based outpatient care, in-home nursing-assisted intravenous infusion can be considered as an alternative option; in such cases, zoledronic acid is preferred over pamidronic acid due to its shorter infusion time (grade D recommendation).

Evidence

In the previously mentioned network meta-analysis, the approved bisphosphonates (zoledronic acid and pamidronic acid) showed a significant reduction in the incidence of skeletal-related events compared with control (placebo or no treatment).[13] However, only zoledronic acid administration showed a progression-free survival benefit (hazard ratio [HR] 0·70 [95% CI 0·52–0·95]) and an overall survival benefit (0·57 [0·43–0·75]) compared with the control.[13] Furthermore, zoledronic acid was not inferior to pamidronic acid in preventing skeletal-related events (ie, reducing the incidence of and delaying time to first skeletal-related event) and reducing bone pain.[23] In a record-based study (not included in the meta-analysis) of 1018 US military veterans diagnosed with multiple myeloma, zoledronic acid reduced the risk of death from any cause by 22% and decreased the incidence of skeletal-related events by 25% compared with pamidronic acid.[24] However, a higher proportion of patients developed osteonecrosis of the jaw in the zoledronic acid group (2·6%) than in the pamidronic acid group (0·8%).[24]

Zoledronic acid is superior to clodronic acid in reducing the incidence of skeletal-related events in patients with newly diagnosed multiple myeloma receiving upfront antimyeloma treatment (265 [27%] of 781 *vs* 346 [35%] of 779; HR 0·74, 95% CI 0·62–0·87; p=0·004, table).[14] This favourable effect was evident irrespective of the presence of multiple myeloma-related bone disease on conventional radiography at diagnosis or as a result of the administration of maintenance treatment with thalidomide.[14,25] In the MRC Myeloma IX trial, zoledronic acid also resulted in a significant reduction of mortality by 16% (HR 0·84, 95% CI 0·74–0·96; p=0·012) and improvement in progression-free survival by 12% (HR 0·88, 95% CI 0·80–0·98; p=0·018) compared with clodronic acid (table).[26] We have to stress that the difference in mortality was mainly due to the reduction of infections in the zoledronic acid group compared with the clodronic acid group. In subsequent subgroup analyses, the overall survival benefit was more pronounced among patients with multiple myeloma who had evidence of multiple myeloma-related bone disease at diagnosis.[25] The antimyeloma activity of zoledronic acid might be partly attributable to either a direct effect of the treatment, by inhibiting protein prenylation, or to an indirect effect, by reducing the expression of bone marrow stromal cell-associated adhesion molecules, with both effects ultimately leading to myeloma cell apoptosis.[27]

Regarding pamidronic acid, a randomised, double-blind trial including 504 patients with newly diagnosed multiple myeloma showed that monthly pamidronic acid 30 mg administration was equivalent to pamidronic acid 90 mg on physical function and median time to first skeletal-related event. Retrospectively, a statistical trend towards reduced osteonecrosis of the jaw and kidney injury risks with pamidronic acid 30 mg versus pamidronic acid 90 mg was reported.[28]

Treatment adherence is a prerequisite for positive outcomes; thus, patient education is considered to be of utmost importance. Intravenous administration of bisphosphonates can be done during a scheduled patient visit. The shorter infusion time of zoledronic acid makes it a more convenient treatment method than pamidronic acid for both patients and hospital staff.[29] Bisphosphonates can also be infused under nursing surveillance at home.[29] Outside the USA, clodronic acid administered orally is an option for cases of incapacity for in-hospital or in-home intravenous bisphosphonate administration.[30]

Duration of treatment

Recommendations

Zoledronic acid should be administered monthly for at least 12 months (grade B recommendation). If, after 12 months, a very good partial response or better is achieved, the treating physician can consider decreasing the dosing frequency to every 3 months or, on the basis of osteoporosis recommendations, to every 6 months or yearly, or even zoledronic acid discontinuation. The decision to stop zoledronic acid in this setting should take into consideration an individualised evaluation of fracture risk based on sex, age, ethnicity, body-mass index, history of fractures, smoking and alcohol drinking status, bone mineral density, systemic disease (other than multiple myeloma) associated with secondary osteoporosis, and daily and cumulative glucocorticoid dose, which is frequent in continuous antimyeloma regimens (panel consensus).[31,32] If, after 12 months, a very good partial response has not been achieved, zoledronic acid has to be continued monthly until a very good partial response or better is achieved. Thereafter, decreasing the dosing frequency or discontinuing zoledronic acid can be applied (grade D recommendation; panel consensus).

Pamidronic acid should be administered in patients with multiple myeloma who have active disease and can be continued at the physician's discretion, taking into consideration the aforementioned patient-related and disease-related factors (grade D recommendation; panel consensus). If discontinued, zoledronic acid or pamidronic acid should be reinitiated at the time of biochemical relapse to reduce the risk of a new bone event at clinical relapse (grade B recommendation).

Evidence

In the MRC Myeloma IX trial, patients receiving zoledronic acid for 2 years or more showed improved overall survival compared with patients receiving clodronic acid, both from time of randomisation and from first disease progression.[25] Extending zoledronic acid administration from 2 years to 4 years did not result in an overall survival benefit in another study including 170 patients with newly diagnosed multiple myeloma.[33] The incidence of skeletal-related events was lower in the 4 year group compared to the 2 year group; however, no data on the quality of multiple myeloma responses were available.[33]

The introduction of novel quadruplet combinations of an anti-CD38 monoclonal antibody, a proteasome inhibitor, an immunomodulatory drug, and dexamethasone in the front-line treatment of patients with newly diagnosed multiple myeloma has been shown to increase the depth of the response by inducing a substantial, durable disease remission.[34] Therefore, the necessity of continuous treatment with bisphosphonates in these patients for more than 1 year is questionable. Consolidation with bortezomib-based regimens after autologous transplantation has shown a favourable effect in bone metabolism and a low skeletal-related event incidence in the absence of bisphosphonate co-administration in two prospective studies.[35,36] Importantly, more than half of the patients in the included studies achieved a complete response or better at the end of consolidation treatment.[35,36] In a retrospective analysis of 1111 transplantation-eligible patients recruited in the MRC Myeloma IX trial, zoledronic acid retained its superiority in skeletal-related event prevention only in the subset of patients achieving a very good partial response or less, on day 100 after transplantation (p=0·048). The overall survival benefit of zoledronic acid over clodronic acid was evident only among patients with a post-transplantation partial response (p=0·0091), but not among those with a complete or very good partial response.[37]

Studies have evaluated whether reductions in bisphosphonate treatment intensity reduce long-term adverse events such as osteonecrosis of the jaw while retaining efficacy. A subgroup analysis of a randomised clinical trial incorporating data from 278 patients with multiple myeloma receiving zoledronic acid, either once monthly or every 3 months, for 2 years, indicated a similar probability of developing at least one skeletal-related event within the 2 year follow-up period.[38] Furthermore, a model based on the concentration of urinary N-telopeptide of type 1 collagen (uNTX), a bone resorption biomarker, was implemented in the Z-MARK study, which evaluated the dynamic adaptation of a zoledronic acid administration schedule according to biomarker concentrations measured every 3 months.[39] Zoledronic acid was given monthly if the uNTX concentration was at least 50 nmol/mmol creatinine and every 3 months if the uNTX concentration was less than 50 nmol/mmol creatinine. This approach resulted in low skeletal-related event rates during the first (5·8%) and second (4·9%) years on the study, and in a 2 year incidence rate of osteonecrosis of the jaw of 3·3%.[39] Reduced uNTX concentrations are associated with fewer skeletal-related events among patients with multiple myeloma in remission who have discontinued zoledronic acid or pamidronic acid, suggesting the potential for less frequent dosing during remission.[40] The 3 month interval of zoledronic acid administration in patients who do respond has also been suggested by the European Myeloma Network and other organisations for the management of multiple myeloma-related bone disease during the COVID-19 pandemic.[41]

Regarding pamidronic acid, a trend towards improved overall survival compared with placebo has been shown at first relapse.[42] Post-transplantation thalidomide maintenance with pamidronic acid did not result in a significant reduction in skeletal-related event occurrence or in an overall survival improvement compared with thalidomide monotherapy.[43] In both treatment groups, a very good partial response or better was achieved in more than 56% of patients.[43]

There is also preliminary evidence showing that patients with multiple myeloma who have been in sustained remission for more than 2 years have a gradual increase in lumbar spine bone mineral density in the absence of bisphosphonate administration.[44]

In a Spanish study, patients at biochemical relapse were randomly assigned to receive either zoledronic acid or no bisphosphonate. The patients had been previously treated with a bisphosphonate, but the treatment had been stopped at first remission.[45] Zoledronic acid did not prolong time to disease progression or survival, but reduced the risk of new bone events at the time of the start of new antimyeloma treatment when compared with no bisphosphonate treatment.

Management of adverse events

Recommendations

Calcium and vitamin D supplementation should be administered to all patients receiving bisphosphonates (grade A recommendation), but only after the normalisation of serum calcium concentration in case of hypercalcaemia. Creatinine clearance, serum electrolytes, and urinary albumin (in patients receiving only pamidronic acid) should be monitored monthly, and dose adjustments should be made accordingly (grade A recommendation). A comprehensive dental examination and any necessary invasive treatment should be done before bisphosphonate initiation (grade C recommendation). Bisphosphonates should be discontinued in case of osteonecrosis of the jaw, unless continued treatment is necessary (eg, if there is progression of lytic bone disease or recurrent hypercalcaemia). 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 can be reinitiated based on individualised risk–benefit considerations (grade D recommendation; panel consensus). Patient education is essential for adherence to dental hygiene and supplement intake, as well as for early recognition and reporting of adverse events (grade D recommendation; panel consensus).

Evidence

Calcium and vitamin D supplementation is important to prevent severe hypocalcaemia, especially in patients with multiple myeloma, in whom vitamin D deficiency is common.[46] Vitamin D is essential for calcium uptake and

normal bone remodelling. The US Institute of Medicine has issued recommendations for calcium and vitamin D daily intake in older healthy adults: 1200 mg per day of calcium for women older than 50 years, 1000 mg per day of calcium for men aged 51–70 years, and 1200 mg per day of calcium for men older than 70 years. For both sexes, the recommended upper dose is 2000 mg per day of calcium. For both women and men, the recommended daily dietary allowance of vitamin D is 600 IU for ages 51–70 years and 800 IU after the age of 70 years, with a recommended maximum of 4000 IU.[47] Patients with renal impairment receiving calcium supplements need close monitoring.

Routine evaluation of renal function is important because bisphosphonates can induce acute renal damage.[23,48] In patients with creatinine clearance between 30 mL/min and 60 mL/min, zoledronic acid and clodronic acid should be administered at reduced doses, and pamidronic acid should be administered with extended duration (ie, 4 h). Zoledronic acid and pamidronic acid should be administered only when creatinine clearance is higher than 30 mL/min, and clodronic acid only when creatinine clearance is higher than 12 mL/min.[49] Reinitiation of bisphosphonates should be considered on restoration of serum creatinine concentrations to within 10% of baseline values. Albuminuria should be monitored during pamidronic acid administration due to the glomerular toxicity of pamidronic acid.[29]

Osteonecrosis of the jaw is an uncommon but debilitating adverse event that has been primarily associated (among users of bisphosphonate) with long-term administration of zoledronic acid.[50–53] However, a meta-analysis did not show an excessive risk of osteonecrosis of the jaw with zoledronic acid compared with other bisphosphonates.[13] Most cases of osteonecrosis of the jaw heal after about 4 months (median, range 2–6 months);[52] therefore, bone-targeted treatment can be restarted, especially in patients with multiple myeloma who develop osteonecrosis of the jaw after a surgical intervention in the oral cavity.[52] Preventive measures are effective in reducing the incidence of osteonecrosis of the jaw.[54,55] Although the documented clinical evidence is scarce, a 6 month periprocedural (3 months before and 3 months after) drug holiday, based on bisphosphonate pharmacokinetics and bone physiology, is suggested for patients undergoing elective invasive dental procedures, especially those responding to antimyeloma therapy.[56] Taking into consideration the long-term exposure to glucocorticoids and the immunosuppressive state of patients as a result of multiple myeloma and antimyeloma treatments, antibiotic prophylaxis such as amoxicillin–clavulanate from 1 day before until 3 days after the invasive dental procedure should be considered.[55] The risk of infection should be evaluated based on dental hygiene, patient comorbidities, and multiple myeloma disease status. Depending on the local clinical practice and the individualised risk assessment, penicillin with or without a β-lactamase inhibitor and metronidazole are possible options. In these cases, a multidisciplinary approach between oncologists, dentists, and oral surgeons is important.[57]

Denosumab

Denosumab is a fully human and highly specific monoclonal IgG2 antibody against RANKL. Denosumab imitates the physiological effect of osteoprotegerin (also known as TNFRSF11B) by inhibiting RANKL interaction with RANK, ultimately decreasing bone resorption.[1]

Indications for treatment

Recommendations

Denosumab is recommended for the treatment of newly diagnosed multiple myeloma (grade A recommendation), and for patients with relapsed or refractory multiple myeloma with evidence of multiple myeloma-related bone disease (grade B recommendation). Denosumab is equivalent to zoledronic acid in delaying the time to first skeletal-related event after a multiple myeloma diagnosis (grade A recommendation). Denosumab might prolong progression-free survival in patients with newly diagnosed multiple myeloma and multiple myeloma-related bone disease who are eligible for autologous stem-cell transplantation (grade B recommendation). Denosumab might be preferable over zoledronic acid in patients with multiple myeloma and renal dysfunction (grade B recommendation). Denosumab can be considered for patients who have creatinine clearance lower than 30 mL/min under close monitoring (grade D recommendation; panel consensus). Denosumab can be also administered in patients with hypercalcaemia related to myeloma, especially in patients who are refractory to zoledronic acid administration (grade B recommendation).

In patients with smouldering multiple myeloma, monoclonal gammopathy of undetermined significance, or solitary plasmacytoma, denosumab is recommended only if there is coexistence of osteoporosis, following osteoporosis guidelines[58] (60 mg subcutaneously, every 6 months; grade D recommendation; panel consensus).

Evidence

The largest study so far to evaluate the comparative efficacy and safety of denosumab versus zoledronic acid in patients with multiple myeloma is the NCT01345019 phase 3 trial (table).[59] This multicentre, double-dummy and double-blind, randomised (1:1) controlled trial included 1718 patients with newly diagnosed multiple myeloma. The study met its primary endpoint of non-inferiority of denosumab compared with zoledronic acid in delaying time to first skeletal-related event (HR 0·98 [95% CI 0·85–1·14]; p=0·010) after a median duration of 17·3 months (IQR 8·9–28·5) for denosumab and 17·6 months (9·4–28·1) for zoledronic acid.[60] This study supported the results of a previous phase 3 trial that had also shown denosumab non-inferiority compared with

zoledronic acid in preventing or delaying time to first skeletal-related event in a subset of 180 patients with newly diagnosed multiple myeloma and relapsed-refractory multiple myeloma (HR 1·03 [95% CI 0·68–1·57]; p=0·89).[60] Because the majority of first on-study skeletal-related events in both treatment groups were reported in the first 6 months in the NCT01345019 trial, an additional analysis at 15 months was done to assess exposure risk of bone-targeted agents. This post-hoc analysis showed that denosumab significantly prolonged the time to first skeletal-related event compared with zoledronic acid (HR 0·66 [95% CI 0·44–0·98]; p=0·039; not estimable for denosumab and zoledronic acid).[59] Furthermore, when denosumab was administered with standard first-line treatment for newly diagnosed multiple myeloma, it improved progression-free survival by 10·7 months compared with zoledronic acid (HR 0·82 [95% CI 0·68–0·99]; p=0·036). In subsequent subgroup analyses, the benefit of denosumab for progression-free survival was particularly evident among patients with an intention to undergo autologous stem-cell transplantation compared with the zoledronic acid group (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.[61,62] However, no difference in overall survival between zoledronic acid and denosumab has been reported so far.

Renal toxicity was more common among patients receiving zoledronic acid (146 [17%] of 852 patients) than among those receiving denosumab (85 [10%] of 850 patients). In patients with renal insufficiency (creatinine clearance 30–60 mL/min), renal adverse events were doubled in the zoledronic acid group (58 [26%] of 220 patients) compared with the denosumab group (30 [13%] of 233 patients).[59] Patients with creatinine clearance under 30 mL/min were not included in the NCT01345019 trial; thus, for this patient group, we can only extrapolate data based on studies of osteoporosis that show the feasibility of denosumab administration regardless of kidney function.[63,64]

Denosumab can be used for the treatment of hypercalcaemia from malignancy that is refractory to bisphosphonates, on the basis of results from a single-arm study that included 33 patients with solid and haematological cancer.[65,66] A pooled analysis of two phase 3 trials has shown that denosumab is superior to zoledronic acid in preventing or delaying the emergence of hypercalcaemia of malignancy in patients with advanced solid tumours and multiple myeloma.[67]

Route of administration, dosing schedule, and duration of treatment

Recommendations

Denosumab should be administered as a subcutaneous injection of 120 mg at monthly intervals (grade A recommendation). Subcutaneous injection at home means that hospital visits can be avoided during the COVID-19 pandemic and makes denosumab administration easier than the intravenous administration of bisphosphonates.[41] Denosumab should be given continuously until unacceptable toxicity occurs (grade A recommendation). Dosing de-intensification, drug holiday, or discontinuation can be considered only after 24 months of treatment and if the patient achieves a very good partial response or better with antimyeloma treatment (grade D recommendation; panel consensus). A tailored evaluation based on patient characteristics, comorbidities, and glucocorticoid use should also guide treatment decisions, as previously discussed with the use of bisphosphonates. Until further data are available on patients with myeloma, a single dose of an intravenous bisphosphonate (eg, zoledronic acid) is recommended at least 6 months after the last denosumab dose to prevent a potential rebound effect; similarly, denosumab administration every 6 months can also be taken into consideration (grade D recommendation; panel consensus).

Evidence

In the NCT01345019 trial, denosumab 120 mg was administered subcutaneously once monthly (median time on study 17·3 months [IQR 8·9–28·5]).[59] Denosumab injection can be given during a routine clinic visit. During the COVID-19 pandemic, subcutaneous administration makes home delivery of denosumab easier compared with intravenous bisphosphonates.[41] Weekly administration for 1 month followed by monthly injections can be considered for patients with zoledronic acid-refractory hypercalcaemia due to multiple myeloma.[66]

Discontinuation of denosumab therapy is not supported by clinical data in myeloma. However, data from the osteoporosis literature has shown that denosumab discontinuation is followed by rebound osteoclastogenesis 6–12 months after denosumab discontinuation, with rapid reduction of bone mineral density and an increased risk of vertebral fractures,[68,69] even in patients who had been previously treated with bisphosphonates.[70] The European Calcified Tissue Society has recommended that denosumab discontinuation be followed by bisphosphonate administration to reduce the rebound effect.[68] In patients with myeloma, it is less certain that the rebound effect will occur, as antimyeloma agents (ie, proteasome inhibitors, immunomodulatory drugs, and daratumumab) have anti-osteoclast activity and counteract bone resorption.[71,72] Nevertheless, taking into consideration that there is no data on the effect and management of denosumab discontinuation in patients with myeloma, by extrapolating the evidence from osteoporosis studies,[1,68] we suggest that a single intravenous dose of zoledronic acid, at least 6 months post-denosumab discontinuation, should be given if a physician wants to discontinue denosumab. Another alternative would be the administration of denosumab every 6 months. Clinical data on this issue are highly needed.

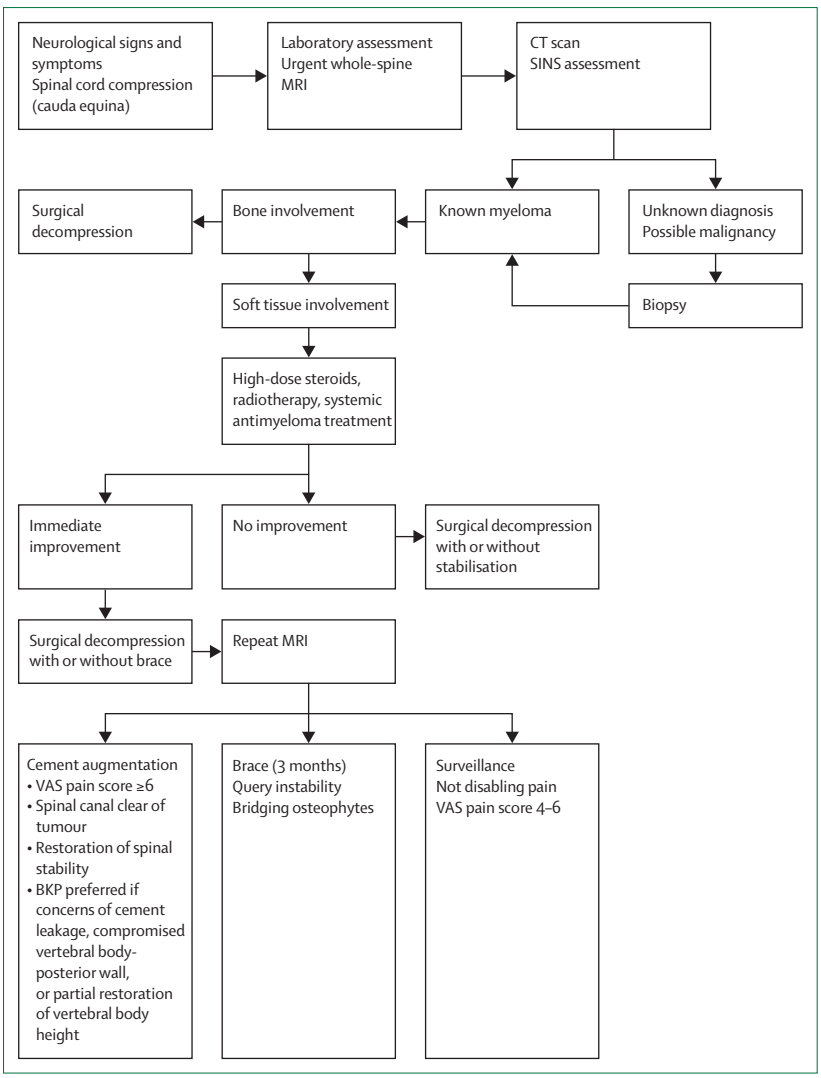

Figure: **Algorithm for the use of cement augmentation, radiotherapy, and surgery in vertebral complications due to multiple myeloma**
BKP=balloon kyphoplasty. SINS=spinal instability neoplastic score. VAS=visual analogue scale.

Management of adverse events

Recommendations

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

Evidence

In the NCT01345019 trial, hypocalcaemia was more frequent with denosumab (17%) than zoledronic acid (12%; table); preventive measures should therefore be taken.[59] Creatinine clearance and serum alkaline phosphatase might predict hypocalcaemia risk.[73] The calcium and vitamin D supplementation recommendations for bisphosphonate also apply here.

Incidence of osteonecrosis of the jaw did not differ between the two groups (35 [4%] of 850 patients in the denosumab group *vs* 24 [3%] of 852 patients in the zoledronic acid group, p=0·15; table), and preventive dental measures are considered to be essential.[59,74]

Other approaches: cement augmentation, radiotherapy, and surgery

Recommendations

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

Evidence

Both prospective[59] and retrospective[75] data have shown that the majority of skeletal-related events occur early, relative to the time of initial diagnosis or relapse. In the NCT01345019 study, 60% of all first skeletal-related events occurred within the first 3 months of the study, with 81% occurring in the first 6 months.[59] Severe pain is a symptom of vertebral fractures in patients with multiple myeloma. Therefore, the immediate effects of bone-targeted agents for skeletal-related event prevention are questionable, and early intervention with other approaches might be necessary. Multiple myeloma-related bone disease burden, presence of osteoporosis, progressive clinical deterioration, history of any skeletal-related events, therapeutic treatment approach, and

treatment duration should be taken into consideration for the characterisation of the high-risk population.[75]

The value of balloon kyphoplasty has been shown in a randomised study including 134 patients with painful vertebral body compression fractures due to bone metastases or multiple myeloma.[76] In the international Cancer Patient Fracture Evaluation study, 70 patients were randomly assigned to receive kyphoplasty along with non-surgical interventions, and 64 patients received only non-surgical management. Balloon kyphoplasty was associated with clinically meaningful improvements in physical functioning, back pain, quality of life, and ability to execute daily activities compared with non-surgical management alone. It is worth noting that less than 10% of patients underwent radiotherapy in both treatment groups. Importantly, these benefits persisted throughout the 12 month study period.[76] Furthermore, several non-randomised studies have shown that kyphoplasty and vertebroplasty are effective in reducing pain scores and restoring functionality in patients with multiple myeloma.[77] The International Myeloma Working Group has recently produced guidelines for the use of cement augmentation in patients with multiple myeloma.[77]

Low-dose radiotherapy (up to 30 Gy) can also be used as a palliative treatment for uncontrolled pain, impending pathological fracture, or impending spinal cord compression (which requires urgent treatment). Radiotherapy is highly effective in pain relief, with up to 90% of patients achieving pain relief.[78] 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 randomised study of 288 patients with widespread bone metastases, including 23 patients with multiple myeloma.[78] No difference in analgesic and recalcification effects between the unifractioned and multifractioned radiotherapy regimens was shown in another randomised study including 101 patients with multiple myeloma.[76] Initial radiotherapy may be followed by cement augmentation to ensure stabilisation of the spine on an individualised basis.[77] However, the treatment sequence does not seem to affect pain improvement.[79]

Orthopaedic consultation should be sought for impending or actual long-bone fractures, bone compression of the spinal cord, or vertebral column instability.[77] Orthopaedic surgical treatment for patients with multiple myeloma-related bone disease is effective in the improvement of symptoms and quality of life. However, these patients have a high risk of perioperative surgical and medical complications (up to 74% complication rate), given that the majority of patients are newly diagnosed and in need of immediate initiation of systemic treatment.[80] In this context, multidisciplinary management is considered to be essential.[80] Although a randomised trial has shown the superiority of direct decompressive surgery followed by radiotherapy compared with radiotherapy alone among patients with spinal cord compression due to metastatic solid cancer, no pertinent randomised data are available on patients with multiple myeloma.[81] Postoperative radiotherapy should be considered, especially for long-bone fractures, to achieve local disease control and prevent failure of the implantation procedure.[82] This approach is particularly important for patients with minimal or no response to systemic antimyeloma treatment.

An algorithmic approach[77] should guide the decision to proceed with kyphoplasty or vertebroplasty, radiotherapy, or surgery, especially in patients with neurological symptoms (figure).

***Panel:* Updated recommendations for the treatment of myeloma-related bone disease**

Patient population

Patients with newly diagnosed myeloma.
Patients with relapsed or refractory myeloma.

Choice

First option

Zoledronic acid (regardless of the presence of myeloma-related bone disease on imaging) for patients with newly diagnosed multiple myeloma or relapsed or refractory myeloma; also consider for patients at biochemical relapse.
Denosumab (only in the presence of myeloma-related bone disease on imaging; also consider for patients with renal impairment).

Second option

Pamidronic acid (when first-option agents are not available or contraindicated).

Administration

Zoledronic acid and pamidronic acid: intravenously.
Denosumab: subcutaneously.

Duration and frequency

Zoledronic acid

Monthly during initial therapy and in patients with less than very good partial response.
If patients achieve a very good partial response or better after receiving monthly administration for at least 12 months, the treating physician can consider decreasing the frequency of dosing to every 3 months or, on the basis of osteoporosis recommendations, to every 6 months or yearly, or discontinuing zoledronic acid.
If discontinued, it should be reinitiated at the time of biochemical relapse to reduce the risk of new bone event at clinical relapse.

Denosumab

Continuously, monthly.
If discontinued, a single dose of zoledronic acid should be given to prevent rebound effects at least 6 months after the last dose of denosumab; also consider giving denosumab every 6 months.

Monitoring and preventive measures

Creatinine clearance and serum electrolytes (monthly) for zoledronic acid, plus urinary albumin (monthly) for pamidronic acid; these tests are not needed for denosumab.
Dental health (at baseline, then at least annually or if symptoms appear) for both bisphosphonates and denosumab.
Calcium and vitamin D supplementation is recommended for all patients for both bisphosphonates and denosumab.
Patient education for early recognition and reporting of adverse events for both bisphosphonates and denosumab.

Conclusion

Bisphosphonates or denosumab should be considered as the standard of care for the treatment of multiple myeloma-related bone disease (panel). The decision to choose one bone-targeted agent over another should include consideration of multiple factors, such as cost, convenience, patient preference, and toxicity profile. Economic models have shown that denosumab is a cost-effective treatment both in the USA[83] and Europe[84] over zoledronic acid. However, these studies have the limitation that the costs were estimated from multiple sources, which varied by patient population, country, and other parameters. Furthermore, progression-free survival and overall survival were extrapolated beyond the follow-up of the primary analysis of the phase 3 study comparing denosumab with zoledronic acid through fitted parametric curves. We suggest that until further data are available, zoledronic acid should be the preferred treatment option for patients who do not have imaging findings for multiple myeloma-related bone disease, whereas denosumab should be the preferred treatment option for patients with renal impairment.

We consider preventive measures to be essential to avoid renal impairment, hypocalcaemia, and osteonecrosis of the jaw as a result of bone-targeted agent treatment. Cement augmentation, radiotherapy, and surgery should be implemented in specific situations, such as spinal cord compression, pain control, and pathological fractures of weight-bearing bones. Ongoing clinical trials are investigating the role of denosumab in patients with creatinine clearance of less than 30 mL/min (NCT02833610). Other novel bone anabolic agents are also currently under investigation.[85]

Contributors

ET, EZ, and NR conceived and designed the paper. ET, IN-S, and NR collected and assembled the data. ET overviewed this study. All authors analysed and interpreted the data. ET, EZ, IN-S, and NR wrote the first draft. All authors had full access to all the data in the study, wrote the final paper, and had final responsibility for the decision to submit for publication.

Declaration of interests

ET has received honoraria from Amgen, Celgene, Genesis, Janssen, Novartis, Bristol Myers Squibb (BMS), and Takeda; is a member of the scientific councils of Amgen and Takeda and a member of the Independent Data Monitoring Committee of Celgene; and has received research grants from Amgen, Janssen, and Takeda. SL has received honoraria from Caelum Biosciences, Sorrento, Janssen, Celularity, Sanofi, AbbVie, Takeda, and Bayer, and research funding from Karyopharm and Sanofi; is a shareholder, patent holder, and board member of Caelum Biosciences, but the company is not involved in, and does not have any products related to, the treatment of multiple myeloma-related bone disease; and is a member of the Data Safety Monitoring Board of Sorrento and Celularity. RG-S has received honoraria from Gilead, Takeda, Roche, BeyondSpring, Novartis, and Janssen-Cilag; has received grants from Janssen-Cilag, Gilead, and Takeda; has received clinical trial expenses from the University of Salamanca; and reports Spanish Society of Haematology as a scientific society with Continuing Medical Education contracts with many companies. FS has received honoraria from Amgen, Celgene, Takeda, Janssen, Novartis, SkyliteDX, Oncopeptides, Sanofi Aventis, and Merck Sharp & Dohme (MSD); and has received grants from Amgen, Celgene, Janssen, and Oncopeptides. JdlR holds consulting and advisory roles for Amgen, Celgene, Janssen, Sanofi, and Takeda; is part of the speakers' bureau for Amgen, Celgene, Takeda, and Janssen; and provides expert testimony for Amgen, Celgene, Janssen, and Takeda. JH has received honoraria from Adaptive, BMS, GSK, Janssen, and Oncotracker. SZ declares participation in advisory boards for Takeda, Celgene, Janssen, and Oncopeptides; and has received research funding from Janssen and Takeda. MC has received honoraria from Janssen, Celgene, BMS, AbbVie, GSK, and Sanofi. PM declares receiving honoraria from Celgene, Janssen, Amgen, Sanofi, and AbbVie. JS-M declares receiving consultancy fees from Amgen, BMS, Celgene, Janssen, MSD, Novartis, GSK, Takeda, Sanofi, Roche, AbbVie, and Karyopharm. MAD has received honoraria from Amgen, Celgene, Beigene, Janssen, BMS, and Takeda. NM declares receiving consulting fees from Celgene, Takeda, Janssen, OncoPep, AbbVe, Adaptive Biotechnologies, Amgen, Beigene, Karyopharm Therapeutics, and BMS. BGMD holds an advisory role for Amgen, Janssen, BMS, and Takeda. NR declares receiving consulting fees from Amgen. All other authors declare no competing interests.

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