Multiple Myeloma (Part 2) – Update on The Approach to Bone Disease

Mieloma múltiplo (Parte 2) – Atualização sobre a abordagem da doença óssea

Alex Guedes[1] Ricardo Gehrke Becker[2] Luiz Eduardo Moreira Teixeira[3]

[1] Orthopedic Oncology Group, Hospital Santa Izabel, Santa Casa de Misericórdia da Bahia, Salvador, BA, Brasil
[2] Orthopedic Trauma Service, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brasil
[3] Locomotor Apparatus Department, Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brasil

Address for correspondence Alex Guedes, MD, MSc, PhD, Rua Marechal Floriano 212/401, Canela, 40.110-010, Salvador-BA, Brasil (e-mail: alexguedes2003@yahoo.com.br).

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Abstract

The increase in life expectancy of the world population has led to a concomitant increase in the prevalence of multiple myeloma (MM), a disease that usually affects the elderly population. Bone lesions are frequent in patients with this condition, demanding an early approach, from drug treatment, through radiotherapy to orthopedic surgery (prophylactic or therapeutic) with the objective of preventing or delaying the occurrence of fracture, or, when this event has already occurred, treat it through stabilization or replacement (lesions located in the appendicular skeleton) and/or promote stabilization and spinal cord decompression (lesions located in the axial skeleton), providing rapid pain relief, return to ambulation and resocialization, returning quality of life to patients. The aim of this review is to update the reader on the findings of pathophysiology, clinical, laboratory and imaging, differential diagnosis and therapeutic approach of multiple myeloma multiple myeloma bone disease (MMBD).

Keywords
- Diphosphonates
- Fractures Spontaneous
- Multiple myeloma
- Prophylactic Surgical procedures
- Orthopedic procedures
- Radiotherapy

Resumo

O aumento da expectativa de vida da população mundial levou a incremento concomitante na prevalência de mieloma múltiplo (MM), patologia que geralmente afeta a população idosa. Lesões ósseas são frequentes nos portadores desta condição, demandando abordagem precoce, desde o tratamento medicamentoso, passando pela radioterapia até a cirurgia ortopédica (profilática ou terapêutica) com os objetivos de prevenir ou retardar a ocorrência de fratura, ou, quando este evento já ocorreu, tratá-la mediante estabilização ou substituição (lesões situadas no esqueleto apendicular) e/ou promover estabilização e descompressão medular (lesões situadas no esqueleto axial), proporcionando rápido alívio da dor, retorno à deambulação e ressocialização, devolvendo a qualidade de vida aos pacientes. O objetivo desta revisão é atualizar o leitor sobre a fisiopatologia, a clínica, exames

Palavras-chave
- Difosfonatos
- Fraturas espontâneas
- Mieloma múltiplo
- Procedimentos cirúrgicos profiláticos
- Procedimentos ortopédicos
- Radioterapia

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laboratoriais e de imagem, diagnóstico diferencial e abordagem terapêutica da doença óssea no mieloma múltiplo (DOMM).

INTRODUCTION

The main clinical manifestations of multiple myeloma bone disease (MMBD) are related to bone destruction.[1,2] Despite progress in antitumor therapy and more aggressive treatments, the incidence of MMBD is still high. Complications such as diffuse osteopenia, osteolytic lesions, pathological fractures, hypercalcemia and bone pain occur in up to 80% of patients with multiple myeloma (MM) at diagnosis and in more than 90% during the course of the disease,[3] constituting the main causes of morbidity.[1,4,5]

The purpose of this article is to update the reader on the approach to MMBD, with regard to pathophysiology, clinical, laboratory and imaging evaluation, differential diagnosis and treatment.

PATHOPHYSIOLOGY

MMBD is characterized by increased resorption on bone formation[1,3,4,6–8] due to overexpression of the receptor activator of nuclear factor kappa B (RANK), its ligand (RANKL) and osteoprotegerin (OPG), resulting in increased osteoclastic activity,[3] that leads to development of lesions without evidence of typical replacement or repair[6–8] and osteoporosis, bone pain, pathologic fractures, hypercalcemia, and spinal cord compression.[3]

Increased Bone Resorption

In MM, bone destruction is mediated by osteoclasts and not by neoplastic cells. Osteoclasts accumulate on resorptive surfaces adjacent to neoplastic cells, and their number is not increased in areas not involved by the tumor. The increase in osteoclastic activity is mediated by the release of osteoclast activating factors produced by neoplastic cells or medullary stromal cells (BMSCs).[1]

Neoplastic cells adhere to BMSCs through a4b1 integrin, present on their surfaces, to vascular cell adhesion molecule-1, expressed in stromal cells.[9] Adhesion of MM cells to BMSCs and osteoblasts increases the production of RANKL, macrophage colony-stimulating factors, and other cytokines that activate osteoclasts, such as IL-6, IL-11, IL-1β, tumor necrosis factors, and factor of basic fibroblastic growth. At the same time, the production of OPG, which naturally occurs and antagonizes the effects of RANKL, preserving bone integrity, is suppressed[1,9] - there is a decrease in OPG production by stromal cells, induced by neoplastic cells, and OPG sequestration by neoplastic cells, which degrade it in their lysosomes; both mechanisms may contribute to the local and systemic reduction of OPG in patients with MM.[1] The RANKL/OPG ratio is determinant in the regulation of bone resorption. The interactive network of cytokines and hormones involved in bone resorption and anti-resorption converge in the RANKL/OPG system, which acts as a common end effector in the regulation of osteoclastic formation from its bone marrow precursors and subsequent activation.[1]

RANK and RANKL play an important role in the development of osteoclasts - RANK is expressed on the surface of these cells; RANKL is expressed on the surface of osteoblasts and stromal cells, and, by binding to its receptor (RANK), it drives differentiation and activation signals in osteoclastic precursors, promoting bone resorption.[1]

IL-1β is a potent stimulator of osteoclast formation, but its levels in patients with MM are very low. This suggests that IL-1β is probably not a major mediator in MMBD.[1,9]

IL-6 stimulates the development of osteoclasts. The use of anti-IL-6 allowed demonstrating the role of this cytokine in stimulating bone resorption in patients with MM.[1]

Other important factors are MIP-1α and MIP-1β chemokines. There is an overproduction of MIP-1α in the bone marrow and both chemokines are secreted by neoplastic cells, acting on the chemoattractiveness and activation of monocytes. Osteoclastic precursors and stromal cells express receptors for MIP-1α and MIP-1β. The chemokine MIP-1α as well as MIP-1β induce RANKL expression in stromal cells and, consequently, increase bone resorptive activity. In addition to their inductive osteoclastic capacity, these chemokines have relevant biological activities in determining other clinical characteristics present in MM patients, acting as potent modulators of hematopoiesis: MIP-1α inhibits early erythropoiesis and MIP-1β increases apoptosis in pre-B cells by suppressing erythropoiesis, B lymphopoiesis, and immunoglobulin production.[1]

Decreased Bone Formation

Histomorphometric studies and biochemical indicators demonstrate that, although the number and function of osteoclasts are increased in the MM, the determining condition for the presence or absence of lytic lesions is lower osteoblastic activity.[1]

In the early stages of MMBD, bone formation is increased, reflecting the coupling of resorption to formation. However, as the disease progresses, bone formation decreases, with rapid bone loss, suggesting that neoplastic cells initially stimulate osteoblastic function and then inhibit it, or there is cellular toxicity during tumor expansion.[1]

Even when MM is in remission, with no evidence of neoplastic cells in the marrow, bone lesions persist. Treatment with bisphosphonates inhibits resorption without inducing bone repair.

The clinical finding that patients with MM have decreased osteoblastic activity has been confirmed in several in vitro and in vivo studies.[9] However, few inhibitory interactions between osteoblasts and MM have been described. MM cells produce the protein dickkoppf 1 (DKK1), which inhibits

osteoblasts. Indeed, DKK1 overexpression in MM is associated with MMBD.[1] Possible candidates for osteoblast inhibitors in MM include DKK1 and other factors that block the Wnt signaling pathway, along with IL-3 and IL-7.[9]

CLINICAL EXAMINATION

MMBD is the leading cause of MM-related morbidity.[10] Patients often have diffuse bone pain, especially around the sternum and pelvis.

The osteopenic state culminates in pathological fractures[6]; > 50% of patients with MM will have fractures during the course of the disease,[2] mainly in the vertebrae, costal arches, pelvis,[1,6,11] skull,[6] and proximal segments of the humerus and femur[1,12] - MM can be diagnosed in this scenario.[11] Fractures significantly compromise quality of life by association with chronic pain and functional disability.[1] Spinal cord compression occurs in up to 5% of patients, leading to pain, paresthesias and paresis in the lower limbs (LL).[11]

A quarter of MM patients have hypercalcemia, more common in the presence of a larger tumor volume, regardless of the protein status related to serum parathyroid hormone - the reasons for this are still unclear, but this fact may be related to the greater intensity of bone resorption produced by the neoplastic cells, as well as the condition of glomerular filtration. Diagnosis is based on ionic calcium concentration, as serum calcium may be low in concentration due to its binding to albumin. It is a serious and potentially fatal condition,[1] the clinical features of which often depend on calcium concentration: patients may be asymptomatic ($\leq$ 3 mmol/l); presenting symptoms such as xerostomia, anorexia and vomiting, polyuria, polydipsia, depression or confusion (3 to 4 mmol/l); or, have a "hypercalcemic crisis" associated with coma ($\geq$ 4 mmol/l).

LABORATORY EXAMINATIONS

It is important to measure ionic calcium and perform tests of renal function and protein electrophoresis.

A critical and sensitive, but nonspecific, laboratory finding is the red blood cells in *rouleaux*, observed in the peripheral slides of patients with MM.[6]

Markers of bone resorption (pyridinoline, deoxypyridinoline, and N-terminal collagen I telopeptide in urine) are increased, while markers of bone formation, such as osteocalcin and alkaline phosphatase, are decreased.[1]

Bone marrow aspiration or biopsy demonstrates the presence of atypical plasma cells.[5]

IMAGING EXAMS

As the main clinical manifestations of MM are related to MMBD, it is important to evaluate the skeleton using imaging tests,[1] making it possible to: detect lesions at risk of fracture; fractures that have already occurred or spinal cord compression; adjust the therapeutic planning; evaluate the evolution of the pathology; and parameterize the evaluation of the response to systemic treatment.[1,12]

Contrary to what is observed in bone metastases (BM) of carcinoma, bone lesions in MM do not usually show reactional new bone formation.[6,10] Approximately 1-2% of patients have extramedullary disease at diagnosis, and in 8% of cases it develops later in the disease course.[10]

MMBD imaging assessment includes whole body radiographs,[1,4–6] ow-dose whole-body computed tomography (CT),[12] magnetic resonance imaging (MRI),[1,4–6,12] whole-body magnetic resonance imaging (WBMRI)[13–16] and positron emission tomography-computed tomography (PET-CT)[6,12,16,17] (►**Figs. 1A-F**, **2E-F**).

Bone scintigraphy (BS) with 99mTc MDP, routinely requested in the investigation of patients with disseminated bone lesions, despite being highly sensitive in detecting BM of breast and prostate carcinoma, does not have the same sensitivity in MM, as lesions not involved by reactive bone usually do not capture[4,15,16]–BS has low sensitivity in detecting osteolytic lesions (37%-60%),[1,5] except in cases where there are associated fractures. The information provided by the BS is useful, however, in the diagnostic direction, suggesting to indicate more adequate imaging methodologies for the staging of this disease.

The advantages and disadvantages of the different imaging tests in the diagnosis of MMBD are summarized in ►**Table 1**.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes monoclonal gammopathy and associated clinical conditions (monoclonal gammopathy of undetermined significance, latent MM, plasmacytoma, Waldenström's macroglobulinemia), polyclonal gammopathy (collagen diseases, cirrhosis, viral exanthems), BM of carcinoma and cystic fibrous osteitis.[5]

INTERNATIONAL MYELOMA WORKING GROUP (IMWG) RECOMMENDATIONS FOR THE TREATMENT OF MMBD[8]

Treatment with Diphosphonates

Diphosphonates are pyrophosphate analogues that bind to exposed areas of hydroxyapatite crystals during the bone remodeling process. They are potent inhibitors of intracellular farnesyl pyrophosphate synthase, leading to osteoclast apoptosis and prevention of bone loss.

Indications

Diphosphonates (zoledronate or pamidronate) should be administered to all patients with active MM, regardless of the presence or absence (only for zoledronate) of identifiable MMBD in imaging studies.

Zoledronate (ZOL) is also indicated in the treatment of MM-related hypercalcemia and is superior to pamidronate (PAM) in this setting.

Choice of Diphosphonate, Route of Administration and Dosing Schedule

In patients with symptomatic MM, 4 mg intravenous (IV) ZOL given over 15 min every 3-4 weeks. 30 or 90 mg IV PAM given

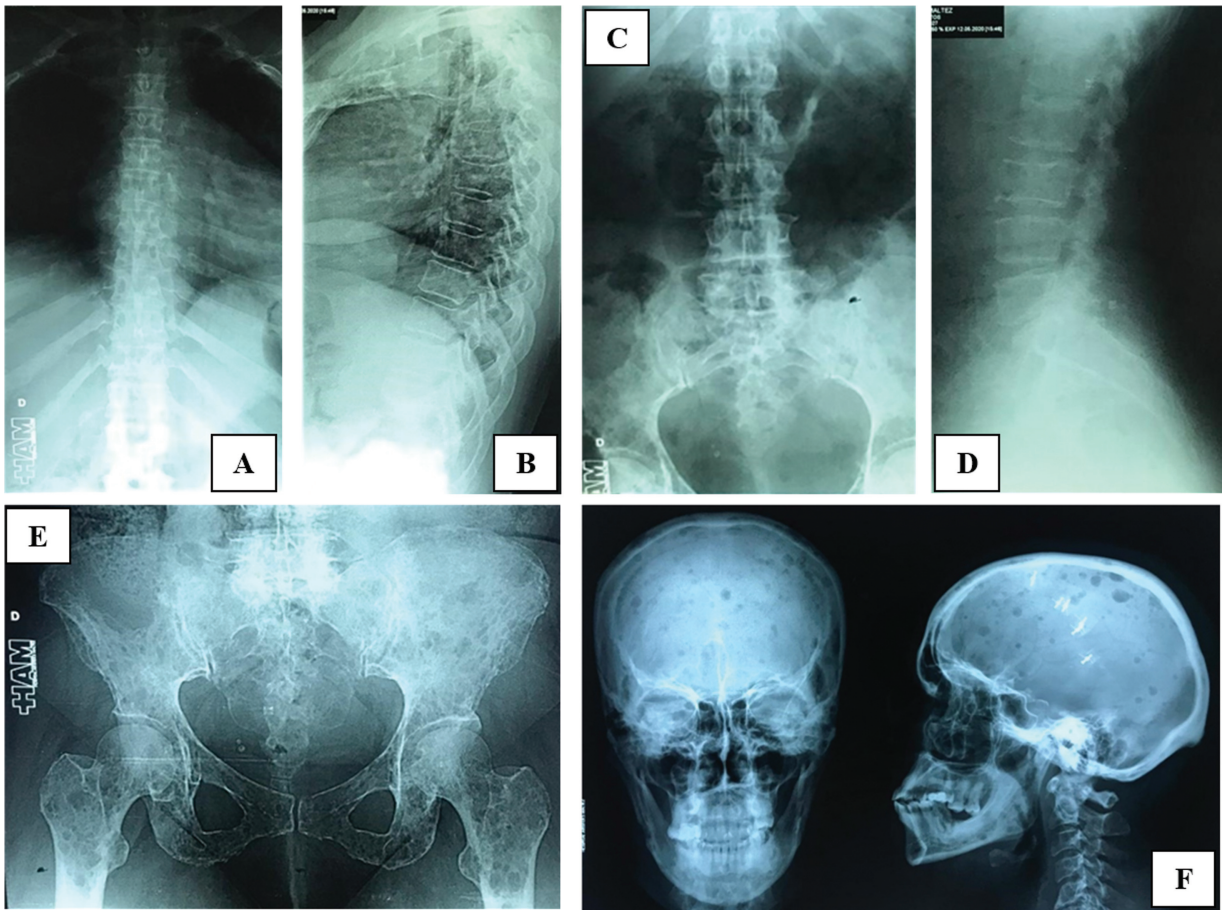

Fig. 1 (A–F) Female patient, 49 years old, black, with MM, with multiple bone lesions in the axial and appendicular skeleton.

every 3-4 weeks for 45 min (for 30 mg) or 2 h (for 90 mg) is recommended for prevention of skeletal related events (SRE). Dose adjustments are essential in case of renal impairment, both at diagnosis and during treatment.

In addition to more convenient administration, ZOL is preferred over PAM because of the significant reduction in the mortality rate. ZOL is also preferred over clodronate (CLO) due to its superiority in reducing SRE and improving survival, especially in newly diagnosed patients and patients with multiple MMBD at diagnosis. Compared with placebo or no treatment, only ZOL showed both progression-free survival and overall survival benefits. PAM 90 mg IV monthly is not superior to PAM 30 mg IV monthly for SRE prevention.

In outpatients, administration of IV ZOL is preferred over IV PAM or oral CLO. In patients unable to receive outpatient care, home infusion may be an alternative; in these cases, ZOL is preferable to PAM, due to the shorter infusion time.

Duration of Treatment

ZOL must be administered monthly for at least 12 months. If, after this period, a very good or better partial response is achieved, one may consider decreasing the frequency to every three months or, based on osteoporosis recommendations, every six months or annually, or even discontinuing it. The decision to discontinue ZOL should consider individualized assessment of fracture risk based on gender, age, ethnicity, body mass index, fracture history, smoking, alcohol consumption, bone mineral density, associated systemic disease (other than MM) to secondary osteoporosis, and daily and cumulative dose of glucocorticoid, frequent in continuous anti-myeloma regimens. If, after 12 months, a very good partial response has not been achieved, ZOL should be continued monthly until this occurs; hence, one can decrease the frequency or stop the treatment.

PAM should be administered to patients with MM who have active disease and can be continued at clinical discretion, taking into account patient and disease-related factors.

If discontinued, ZOL or PAM should be restarted on relapse to reduce the risk of new SREs.

Adverse events

Calcium and vitamin D supplementation should be performed in all patients receiving diphosphonates, but only after normalization of calcium concentration, in the case of hypercalcemia. Creatinine *clearance*, serum electrolytes, and urinary albumin (in patients receiving PAM only) should be monitored monthly, with dose adjustments accordingly.

A comprehensive dental examination and any necessary invasive treatment should be performed prior to initiation of therapy. Diphosphonates should be discontinued when osteonecrosis of the jaw is present, unless ongoing treatment is required (MMBD progression or recurrent hypercalcemia).

Table 1 Advantages and disadvantages of different imaging modalities in the diagnosis of MMBD

Imaging Examination	Advantages	Disadvantages
Whole-body radiographs	Cost; readily available; detects skull and limb injuries - findings consist of punch injuries, osteoporosis, or fractures in 75% of patients.	Low sensitivity and positivity; detects lesions only after apparent bone destruction (30 to 50% bone loss); discomfort due to positioning and repetitive exams; the image collection process is slow.
Whole-body low-dose CT	High sensitivity and positivity; allows aspiration biopsy and surgery guided by 3D images; defines radiotherapy planning; demonstrates the measurement of extramedullary lesions, detects bone marrow invasion and osteolysis; allows to evaluate the tumor load; data collection is fast; lower cost than MRI or PET-CT; little discomfort for the patient.	Cost; may miss skull and costal arch injuries; difficult determination of the number of injuries; when lytic bone lesions are not identified, the negative predictive value is low (59%), not excluding the diagnosis, requiring follow-up and complementation with MRI, WBMRI and/or PET-CT.
MRI	There is no exposure to radiation; allows locating and measuring infiltrative lesions in the bone marrow and focal lesions; it allows accurately diagnosing eventual spinal cord compression; the number of lesions may indicate prognosis; displays extramedullary lesions; 3D reconstruction imaging can help with biopsy and planning surgery and radiotherapy.	Cost; lengthy process for data collection; unsuitable for patients with claustrophobia or metal implant wearers; the drug used as a contrast agent is contraindicated in patients with severe renal impairment; bone marrow infiltration may be misdiagnosed as an osteolytic lesion; presence of electric field limitations and motion artifacts.
WBMRI	No ionizing radiation or need for contrast; faster image acquisition than PET/CT; well tolerated; superior spatial resolution; High accuracy in the study of bone marrow, especially when there is no detectable bone destruction on radiographs or CT; more sensitive than PET-CT in detecting bone involvement; better differentiation between therapeutic response and disease progression; provides information with prognostic value (number and extent of lesions, prediction of fracture risk).	Cost; accessibility and availability; time for image acquisition may require sedation; as it is a very sensitive methodology, it may lead to unnecessary tests and biopsies; same contraindications as MRI.
PET-CT	Reflects the activity of the lesions; it allows evaluating the activity of the lesions in the pre and postoperative period; extramedullary lesions can be imaged; it facilitates the evaluation of the prognosis in the pre and postoperative period; the use of new radionuclides makes it possible to identify different diseases.	Cost; accessibility and availability; low resolution in lesions smaller than 0.5 mm; MM insensitive with low fluorodexyglucose activity; limited diagnostic value (false-positive results due to inflammation, infection, fractures, bone remodeling, post-surgical or post-biopsy changes, recent chemotherapy and radiotherapy).

Abbreviations: 3D, three-dimensional; MM, multiple myeloma; PET-CT, positron emission tomography-computed tomography; MRI, magnetic resonance; WBMRI, whole body MRI; CT, computed tomography.
Source: Translated and modified from Committee of Surgeons of the Chinese Myeloma Working Group of the International Myeloma Foundation. Consensus on surgical management of myeloma bone disease. Orthop Surg. 2016;8(3):263-269.

If possible, diphosphonates should be temporarily withheld before and after any tooth extraction or invasive oral procedures, and periprocedural antibiotic prophylaxis should be considered; after that, the treatment can be restarted considering risk-benefit. Patient education is essential in adhering to oral hygiene and supplement consumption, as well as in recognizing and reporting adverse events early.

Treatment with Denosumab

Denosumab is a human monoclonal IgG2 antibody, highly specific against RANKL. This drug mimics the physiological effect of OPG, inhibiting the interaction between RANKL and RANK, decreasing bone resorption.

Indications

Denosumab is recommended in the treatment of newly diagnosed MM and in relapsed or refractory cases with evidence of multiple MMBD. It has an effect equivalent to ZOL in delaying the first SRE after the diagnosis of MM. Denosumab may prolong progression-free survival in patients with newly diagnosed MM who are eligible for autologous stem cell transplantation. Denosumab may be preferable to ZOL in the treatment of patients with MM who have renal dysfunction, and may be considered in the treatment of patients who have a creatinine clearance of less than 30 ml/min under close monitoring. Denosumab can also be given to patients with MM-related hypercalcemia, especially those refractory to ZOL.

Route of Administration, Dosage Schedule and Duration of Treatment

120 mg of denosumab should be administered subcutaneously (SC) at monthly intervals. Home SC injection makes administration of denosumab more convenient than IV administration of diphosphonates. Denosumab should be administered continuously until unacceptable toxicity occurs. De-escalation, pause or discontinuation of the drug can only be considered after 24 months if the patient

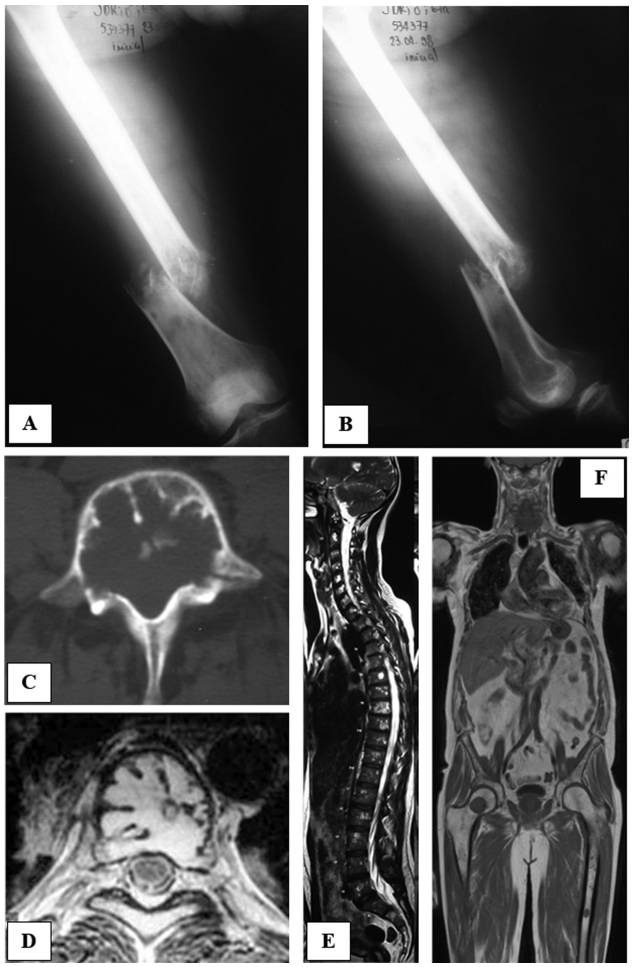

Fig. 2 (**A–F**) (**A, B**) Radiographs in anteroposterior and lateral views of the right femur of a male patient, 67 years old, black, with MM. A pathological fracture of the distal diaphyseal segment of the femur is observed; (**C, D**) CT and MRI of the thoracic spine (axial section) demonstrating osteolysis of the vertebral body (mini brain); (**E,F**) WBMRI demonstrating multiple lesions in vertebral bodies (sagittal section), pelvis, and femur (coronal section).

achieves a very good or better partial response with anti-myeloma treatment. A personalized assessment based on patient characteristics, comorbidities and glucocorticoid use should also guide therapeutic decisions. Until more data is available, a single dose of IV diphosphonate is recommended, at least six months after the last dose of denosumab, to avoid a rebound effect; similarly, the administration of denosumab every six months can be considered.

Adverse Events

Calcium and vitamin D supplementation is recommended for all patients, especially those with renal impairment after normalization of serum calcium concentration, in case of hypercalcemia. Calcium, vitamin D, phosphate and magnesium should be measured regularly to assess the need for supplementation. Oral health should be assessed at baseline and during treatment. Denosumab should be discontinued 30 days prior to invasive dental or oral procedures until healing occurs, at which time it can be restarted.

Radiotherapy

MM cells are radiosensitive and many people with this disease will need radiotherapy at some point, particularly in the treatment of symptomatic bone lesions[1] - radiotherapy is highly effective in relieving pain; up to 90% of patients achieve pain control with this therapeutic approach.[17]

Spinal cord compression occurs in 10% to 20% of patients with MM. In cases where there is no vertebral instability, the use of corticosteroids associated with radiotherapy may prevent permanent neurological deficit.[1]

Radiation therapy may be followed by vertebroplasty/kyphoplasty to ensure vertebral stabilization,[18,19] however, the treatment sequence does not seem to affect the improvement of pain.[19]

The IMWG recommends that radiotherapy should be considered when there is persistent uncontrolled pain, associated with impending or ongoing spinal cord compression, or pathological fractures; in these scenarios, low-dose radiotherapy (above 30 Gy) can be used as a palliative treatment.[8]

Orthopedic Treatment

In general, the orthopedic approach to MMBD is surgical, reserving non-surgical treatment (plastered immobilizations, braces, vests together with drug treatment and/or radiotherapy) for minor injuries that affect the upper limbs (►**Fig. 3A**) and the axial skeleton, accompanied or not by conservatively treatable bone pain not associated with neurological deficits.

More than 90% of patients with MM develop lytic bone lesions that can be surgically treated.[3] The objectives of surgical treatment are: to relieve pain[3,7,8]; maintain function[3,7,8]; improve quality of life[3,7,8] by addressing impending or existing pathological fractures, focal bone lesions associated with refractory pain, medullary and radicular compression, and vertebral instability[3,7,8]; and, (4) need for percutaneous or open biopsy (in 6% of cases, the myelogram is insufficient to establish the diagnosis).[12]

Extensive bone destruction is a surrogate marker of advanced disease and, in general, surgical interventions in these patients may result in a greater number of perioperative complications.[3] Most newly diagnosed patients demand immediate initiation of systemic treatment, impairing immune function. They are usually elderly, many of whom have diabetes and hypertension, in addition to presenting hypercalcemia, anemia, coagulopathies and hypoproteinemia. In particular, care must be taken when correcting anemia; procedures should not be performed until a hemoglobin concentration and platelet count of 10 g/l and 80×10^9/l respectively have been achieved.[13] In this context, multidisciplinary management is considered essential.

Postoperative radiotherapy should be considered,[2,8] especially in long bone fractures, to obtain local control of the disease and prevent failures in procedures involving implants. It is particularly important in those patients who have minimal or no response to systemic treatment.[8]

Staging and prognostic estimation methods that allow categorically defining which patients are eligible for surgical

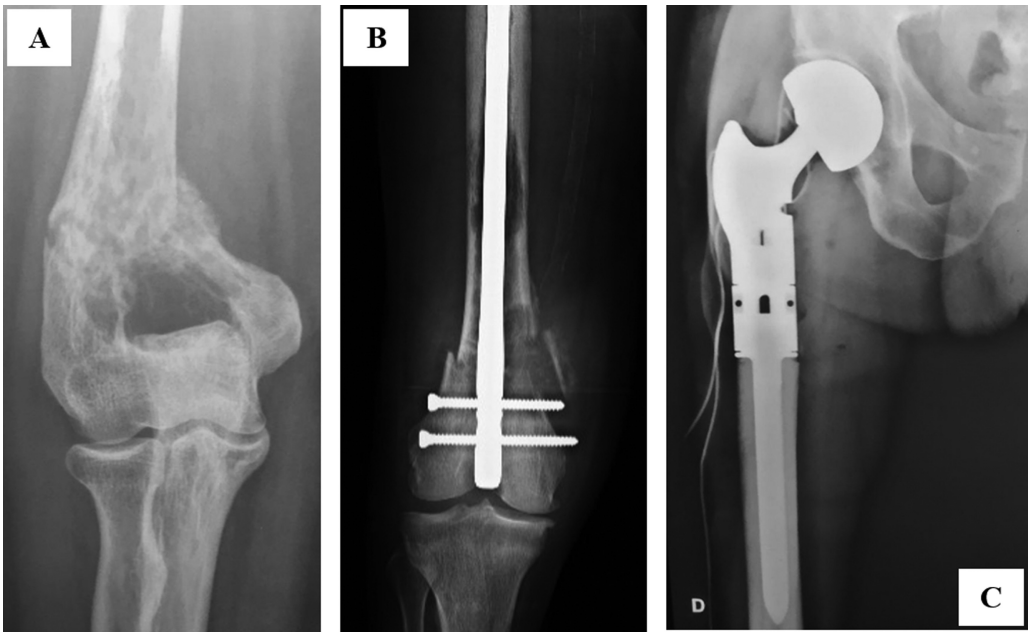

Fig. 3 Orthopedic approach in the treatment of bone lesions associated with MM with imminent or ongoing fracture. (**A**) Nonsurgical treatment of fracture of the distal segment of the right humerus; (**B**) IMN in the treatment of metaphyseal fracture and distal diaphyseal bone lesion in the right femur; (**C**) Modular megaprosthesis in the treatment of an extensive lesion affecting the proximal segment of the right femur.

treatment have not yet been established.[6,12] MM should be staged pre- and postoperatively according to the Revised International Staging System (R-ISS).[6,10,20] Neurological function should be graded using Frankel[12] or American Spinal Injury Association (ASIA) scores, along with assessment of bladder, bowel, and sexual function. Pain should be assessed using the visual analogue scoring system and function using the Karnofsky functional scale[12] or the Eastern Cooperative Oncology Group (ECOG) score.[4] All of these assessment systems are useful for estimating pre- and postoperative therapeutic benefits.[9]

The Committee of Surgeons of the Chinese Myeloma Working Group (CMWG) contraindicates surgical treatment when there is poor clinical condition, intractable cardiac, pulmonary and renal dysfunctions, severe coagulation disorders - which are difficult to control, and severe and uncontrollable infection.[12]

General anesthesia is often the approach of choice because intraspinal blocks and other methods of anesthetic induction are invasive and can lead to bleeding[3,12] and infection.[12] Patients with MMBD are generally in poor physical condition - general anesthesia allows better control of blood pressure, oxygen saturation and respiratory rate.[3,12]

The implants used should preferably be made of titanium alloys or be carbon fiber reinforced as they generate significantly less artifacts than those made of stainless steel. Although titanium alloy implants generate fewer artifacts, the difficulty in properly planning radiotherapy remains, especially in identifying the target and evaluating the amount of dose actually administered to the tissues. Carbon fiber reinforced implants are chemically and biologically stable and allow for even better CT and MRI imaging – these features facilitate monitoring of pathologic fracture healing, local recurrence, progression, and response to treatment,[21] in addition to making it possible to outline an ideal radiotherapy strategy, as the image quality provided during planning reduces discrepancies between late/delivered and measured doses, generating more homogeneous dose distribution[22]; due to their low atomic number and similar radioactive properties to surrounding tissues, they are inert to ionic irradiation and provide minimal disruption to their distribution during radiotherapy.[21]

Pelvic and Periacetabular Injuries

Pelvic and periacetabular involvement in MM has unique characteristics in terms of biomechanics, morbidity, overall survival and prognosis, reflecting on the quality of life of affected individuals.[23] Periacetabular injuries are particularly challenging and are often associated with severe pain, functional disability and pathological fractures; due to load transmission, lesions that show progressive growth can compromise the stability of the pelvic ring.[24]

In MM, pelvic and periacetabular bone involvement occurs in about 6% of cases. The Harrington classification (1981) is widely used in defining the treatment of BM of carcinoma or MM that affect the acetabulum.[25] Group I comprises lesions that present intact subchondral bone; in group II, there is destruction of the medial wall, but demonstrate an intact acetabular roof and lateral wall; in group III, there is destruction of the medial wall, roof and lateral edge of the acetabulum; group IV is defined by the presence of solitary lesions that can be resected en bloc, with anticipation of healing.[24]

Operative treatment is indicated for patients with MM who have periacetabular bone lesions whose non-operative treatment has failed, in pathological/imminent fractures,[24,26] in pelvic collapse, or when the symptoms are intolerable.[24] Expected survival should exceed surgical

recovery time, allowing for a real improvement in quality of life.[24] The surgical approach to these lesions has historically consisted of cementoplasty for contained lesions and Harrington reconstructions for larger and more destructive lesions.[24] In 1981, Harrington described a technique involving the use of threaded Steinmann pins and polymethylmethacrylate for the reconstruction of acetabular defects, associated with cemented total hip arthroplasty, allowing the transmission of load-bearing forces to the intact segment of the pelvis.[24] Due to the limitations of these techniques, new surgical approaches, dictated by the size and location of these lesions, have been created to manage this challenging condition.[26] The use of adjuncts to the Harrington procedure, such as restricted overlays and dual mobility bearings, has reduced historically high rates of prosthetic dislocation.[26] Despite functional improvements and pain control, these procedures are associated with extensive surgical wounds and massive blood loss, leading to the development of percutaneous approaches (including acetabular screw fixation and screw-associated cementoplasty) to minimize surgical morbidity.[24] Antiprotrusion ring with medial wall cementation and acetabular impaction bone graft combined with cementless acetabular components are other well-established methods indicated for contained defects or when acetabular fixation is feasible.[25] Cages and porous tantalum implants are becoming increasingly common in the management of large bone defects and destructive periacetabular injuries.[24] More recently, customized prostheses, developed from the analysis of three-dimensional reconstruction imaging studies, have been used to replace pelvic segments in selected cases.[24]

Spinal injuries

MM is the most common malignancy of the spine,[27] accounting for approximately 15% of all cases.[2] About 70% of patients with MM have spinal injuries,[18] which is the most frequent site for fractures[1] ($>$ 50%)[27]–8 to 10% of patients develop neurological deficits.[2,12,27]

The surgical indication is based on the neurological, oncological, mechanical and systemic (NOMS) decision-making framework, which includes the neurological status (myelopathy, degree of epidural spinal cord compression), radio/chemosensitivity of the tumor, mechanical instability, extension of the systemic disease and comorbidities.[28]

Vertebroplasty and kyphoplasty are indicated for patients with lytic lesions[3] and/or symptomatic compressive vertebral fractures[8] not associated with spinal cord compression.[1,11,12] These procedures provide immediate pain relief and stabilization of the vertebral bodies.[1,12] It is essential to obtain tissue samples during the approach, seeking greater definition or correction in the diagnosis.[12]

Vertebroplasty consists of the percutaneous injection of polymethylmethacrylate (PMMA) into the affected vertebra, under radioscopic control. This procedure allows a significant decrease in pain (up to 97%) but presents a (low) risk of cement leakage and pulmonary embolism.[1]

Kyphoplasty provides vertebral stabilization, pain relief and restoration of vertebral body height. This is possible by inserting a balloon into the affected vertebra which, when inflated, creates a cavity in the vertebral body where PMMA is injected. The frequency of cement leakage is lower with this procedure.[1]

The open approach to the spine is indicated when there is spinal instability, associated or not with spinal cord compression.[3] The procedures are defined according to the number, location and size of the lesions. Approaches include direct anterior, posterior, or combined approaches. The goals of treatment are: removal of as much tumor as possible, decompression, reconstruction and stabilization.[15,16] The implants (titanium alloy or carbon fiber reinforced) are chosen to meet the specific requirements of each procedure, including plates, pedicle screw systems, lateral mass screw fixation systems, artificial vertebral bodies and cages, as well as filling material, such as PMMA and allograft. In addition to facilitating modeling, PMMA has a local adjuvant function, due to the exothermic reaction, which destroys tumor cells - it is therefore the first choice for filling bone defects after tumor removal - autologous bone grafts are not recommended, because they are more prone to resorption.[12]

Combinations of open and minimally invasive surgery are used in the treatment of patients with multiple vertebral injuries, allowing to add advantages presented by both, reducing the need for volume replacement and preventing other complications. Wide or radical resection is unnecessary in the treatment of MM that affects the spine.[12]

Long Bone Injuries

In MM, long bone fractures are relatively less frequent than vertebral fractures, but they usually require hospitalization for early intervention,[6] through fixation or replacement of the affected segment.[1]

Prophylactic surgery has become a reality with the increasingly early diagnosis of MMBD. This approach provides early stability, providing less time for recovery of function when compared to non-surgical treatment.[5] Mirels (1989)[29] developed a risk prediction score for pathological fractures in injuries located in the appendicular skeleton.[6,29–31] This score is based on four characteristics, which are assigned progressive scores from 1 to 3, added at the end: (1) lesion site; (2) nature of the injury; (3) lesion size; and (4) pain (►**Table 2**).[30,31] Based on this score, a recommendation for or against prophylactic surgery is given. Lesions with a score

Table 2 Mirels scoring system

		Score	
Component	*1*	*2*	*3*
Site	Upper limb	Lower limb	Pertrochanteric
Pain	Mild	Moderate	Severe
Lesion	Blastic	Mixed	Lytic
Size	$<$ 1/3 of cortex	1/3–2/3 of cortex	$>$ 2/3 of cortex

Source: Mirels H. Metastatic disease in long bones: a proposed scoring system for diagnosing impending pathologic fractures. Clin Orthop Relat Res. 1989;249:256–264.

equal to or greater than 9 constitute an indication for a surgical approach.[29–31] Lesions with a score of 7 or less can be managed conservatively (observation, radiotherapy and/or pharmacological treatment).[29–31] A score of 8 represents a dilemma - the probability of fracture is only 15%, it is recommended to use clinical judgment for each situation, considering the benefits of prophylactic surgery versus the probability of fracture - more detailed imaging exams allow more accurate access to the dimension of the defect generated by the lesion.[6,29–31]

Pathological fractures of the long bones must be operated on as soon as possible, particularly those in the lower limbs, due to load bearing.[6] Procedures include resection of the affected segment ("expendable" bones), filling with PMMA, internal fixation (screws, plates or intramedullary rods in carbon fiber reinforced or titanium implants)[6,7,11,12,24] or replacement with conventional prostheses[16] or megaprostheses.[1,7,11,15,16]

The choice of surgical procedure depends on the general condition and life expectancy of the patient, previous response to chemotherapy, affected site, number, size and location of lesions and extent of bone invasion.

If there are concomitant lesions in the distal and proximal segments of the same bone, choose long plates or intramedullary nails (IMN). IMN (►**Fig. 3B**) reinforce the affected bone with a definitive, durable and mechanically stable implant, allowing for reduced pain and early discharge.[24,32] Reaming should only be performed when there is good bone quality. The rate of reoperation due to infection, pseudarthrosis or loosening is substantially lower when using IMN, compared to other methods, as it provides greater stability and vascular preservation in bones affected by primary osteoporosis, or secondary to MMBD.[6] Diaphyseal and metaphyseal fractures of the femur and humerus usually require fixation with IMN followed by radiotherapy.

In cases where there is more extensive bone destruction affecting the joint and/or metaphyseal segment of the affected bone,[3] resection with replacement by megaprostheses may be considered (►**Fig. 3C**).[1] Megaprostheses of the proximal segment of the femur provide good functional outcomes, low incidence of complications and better quality of life in the medium term - patients with pathological fracture of the proximal segment of the femur due to MM, confirmed or imminent, treated by resection with replacement, have significantly longer survival.

Although different types of surgeries can provide pain relief and functional improvement in different anatomical locations, the best results, with lower complication rates, are observed in lesions located in the upper extremities[3,12] or diaphyseal segments of long bones.[12]

FINAL CONSIDERATIONS

A proper approach to MMBD is essential for pain control and functional restoration, providing an improvement in quality of life. Therefore, it is necessary to understand the pathophysiology, clinic, laboratory and imaging evaluation, differential diagnosis and treatment associated with this condition.

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Conflict of interests
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