

Bone Disease in Mastocytosis



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KEYWORDS

- Mastocytosis • Osteoporosis • Osteosclerosis • Fracture • Bone mineral density
- Bone turnover markers

KEY POINTS

- Systemic mastocytosis often involves bone, mainly as osteoporosis and fragility fractures.
- In patients with otherwise unexplained osteoporosis or fragility fractures, systemic mastocytosis should be ruled out.
- Risk for vertebral fractures is high, especially in men.
- Bone turnover markers and bone mineral density must be evaluated in each patient, and radiographs of the axial skeleton should be performed to screen for vertebral fracture.
- Traditional risk factors for osteoporosis should be corrected.
- Currently bisphosphonates are the first-line pharmacologic treatment of osteoporosis.

EPIDEMIOLOGY

Bone involvement is one of most common expressions of systemic mastocytosis (SM) in adults. The range of clinical pictures is wide: from osteoporosis with fragility fractures and poorly localized bone pain to asymptomatic osteolytic and/or focal sclerotic lesions and diffuse osteosclerosis. Despite the importance of these aspects, it has only been in the last few years that large epidemiologic studies have been published,^{1–7} also supported by ever increasing extensive use of the dual-energy X-ray absorptiometry (DXA) technique, the gold standard for assessing bone mineral density (BMD).⁸

The prevalence of osteoporosis as defined by the World Health Organization (T score, standard deviation [SD] below the mean of young healthy adults less than -2.5)⁸ in SM varies from 8% to 41% (Fig. 1). It must be emphasized that most of these studies included elderly patients, and this could be a possible confounder

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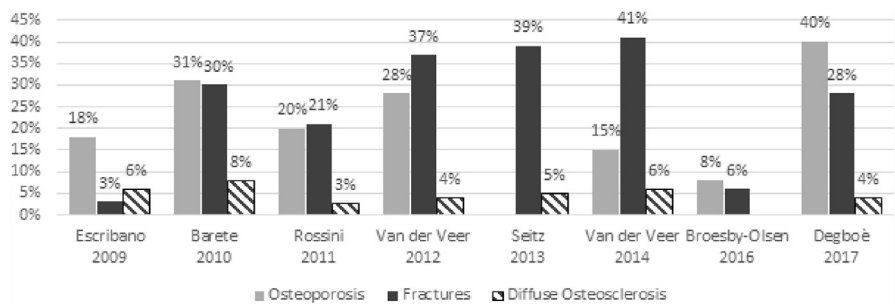


Fig. 1. Prevalence of main bone manifestation in the largest related available studies.

of the real prevalence esteem. Other possible biases could come from data obtained by the health care system, where only clinical evident fractures and osteoporosis were reported,⁷ or from cohorts including a significant proportion of advanced SM (advSM).⁶

The Z score (SD less than the age- and gender-matched mean reference value) is the most appropriate parameter of bone involvement in secondary osteoporosis, as stated by the International Society for Clinical Bone Densitometry.⁹ An inappropriate low bone mass in this case is defined as a Z score lower than -2 .

In the authors' 2011 study on indolent SM (ISM), the prevalence of T scores defined as osteoporosis was 20%, whereas using Z score less than -2 was 9% in women and 28% in men.³ This gender difference has been reported by others,^{1,5} and, interestingly, a study involving men with idiopathic osteoporosis who underwent bone biopsy found a 9% prevalence of SM.¹⁰

The use of Z score helps to correct the above-mentioned confounder, and it changes the proportions, showing a much higher prevalence of inappropriately low BMD in men (Fig. 2 relative to an updated authors' cohort). Data on BMD, a surrogate of bone fragility, confirm data on vertebral fractures that are significantly more prevalent in men than women (20% vs 14%, see Fig. 2), as also reported in other populations.^{1,3,5}

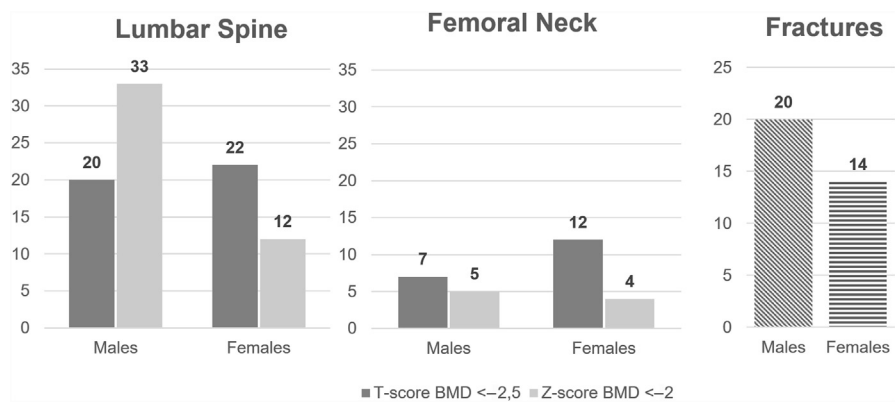


Fig. 2. Prevalence of mastocytosis-related low bone mass, osteoporosis, and fractures according to different criteria in authors' cohort. (Adapted from Rossini M, Zanotti R, Viapiana O, et al. Bone involvement and osteoporosis in mastocytosis. *Immunol Allergy Clin N Am* 2014;34(2):385; with permission.)

The prevalence, which included all types of bone involvement, in the authors' series of ISM was 36%; this is lower than that reported by Barete and colleagues⁴ or Degboe and colleagues,⁶ which also included advSM, which has a more extensive systemic burden and poorer prognosis. Interestingly, in the authors' experience, patients without a history of anaphylaxis showed a lower total hip Z score than patients with a history of anaphylaxis, possibly reflecting a higher diagnosis delay due to the lack of revealing symptoms.¹¹

A study reporting data of a Danish cohort² composed of 157 patients with ISM also described a high incidence of vertebral fractures. Variables associated with fractures and thus inserted in a risk calculator were higher age, male gender, high serum C-terminal telopeptide of collagen I (CTX), lower hip T score, absence of urticaria pigmentosa (UP), and alcohol consumption.^{1,3,5}

These data on UP could find its explanation in an earlier diagnosis of patients with UP and thus a lesser bone burden of disease. However, other investigators did not report the same association.⁶

A rarer bone manifestation of SM is osteosclerosis, which could be local or diffuse, with a total prevalence of the diffuse form ranging from 2.5% to 8%,^{1-5,12} and with a strong predominance among women.¹³ Its prevalence is probably underestimated because of the absence of symptoms and the need for whole skeleton radiographs for detection.

So far there have been no reports of fragility fractures in patients with the sclerotic ISM-related form. However, a coexistence of focal lytic and sclerotic lesions is possible.^{2,4} In a study including 75 adult patients with SM, a mixed pattern was seen in 4%.¹⁴

A limitation in the evaluation of the bone burden of the disease lies also with the fact that almost all the available studies have a cross-sectional design. Longitudinal studies need to be carried out in order to understand the evolution of bone involvement in SM.

Another point that needs to be investigated is bone health in patients with nonclonal mast cell (MC) disorder (mast cell activation syndrome). Data on osteoporosis and fractures prevalence in this subset of MC disease are almost nonexistent, but it is possible that this population also has an increased risk of bone loss and fractures because of the effect of mediators on bone. The only data available are from Alvarez-Twose and colleagues¹⁵ with a 10% prevalence (2 out of 20 patients) of osteoporosis compared with 24% in ISM without skin lesions and 16% of ISM with skin lesions ($P = \text{NS}$), but the numbers are too small to draw any conclusions.

PATHOPHYSIOLOGY

Bone loss seems to affect trabecular bone more than cortical bone, as demonstrated by a higher prevalence of osteoporosis identified at the lumbar spine than at hip (see [Fig. 2](#)) and by a much higher rate of vertebral rather than nonvertebral fractures. The reason of predilection for trabecular bone probably resides in direct colonization of bone marrow by MC with local effects, or the mediators may influence the type of bone more with greater metabolic activity. However, cortical bone can also be affected,⁶ with data reporting a high incidence of nonvertebral fractures as well.¹

The hypothesized mechanisms of bone loss in SM vary and could be related either to total number or to higher activity of MC.¹⁶

Among the mediators released by MC are histamine, heparin, tryptase, and cytokines, such as tumor necrosis factor- α , interleukin-1 (IL-1), IL-17, and IL-6, with effects on both osteoblasts and osteoclasts.^{14,17-20} Increased serum levels of IL-6 have been

reported to correlate with disease progression,²¹ which is also associated with a higher bone burden.

Histamine is one of the distinguishing products of MC, and it is not only involved in the pathophysiology of many SM extraskelatal manifestations but also affects osteoclasts and their precursors, by autocrine and paracrine signaling.^{19,20} Mice knocked-out for an enzyme key for histamine production were protected from postovariectomy bone loss and showed a reduced number of osteoclasts.²² A positive correlation has also been reported between histamine metabolites and risk of osteoporotic manifestations.^{1,5}

Male gender has been reported as a risk factor for osteoporosis and fractures in ISM,^{1,3} suggesting that the mediators could act differently depending on the gender hormonal environment.

Bone histomorphometric data are scarce; however, the little evidence available reports an increased^{12,23} or normal²⁴ number of osteoclasts. A quantitative histomorphometric evaluation applied to a large population of patients with ISM¹² found a decrease in bone trabeculae and an increase in osteoid and bone cellularity (osteoclasts and osteoblasts) that was similar in patients with or without skin involvement.

SM-induced osteoporosis shares some histomorphometric features with the much more common glucocorticoid-induced osteoporosis (GIOP). In fact, in both there is a reduction in the number and the thickness of trabeculae. However, in GIOP, osteoblasts are reduced, whereas in ISM-related osteoporosis, they are not, and bone turnover is significantly increased instead. Of great interest is that osteoclast and osteoblast numbers increase not only with the number of MC but also with the tendency of MC to create granuloma-like groups rather than to be scattered.¹²

Recently, studies on the bone marrow niche suggest a defect of bone marrow stromal cells due to either c-kit mutation of stromal cells as well, or an impaired differentiation toward the osteogenic lineage but not toward the adipogenic one.^{25,26}

Even if histomorphometric analysis is the gold standard for bone metabolism evaluation, in clinical practice, serum bone turnover markers (BTM) are widely used as surrogates. Systemic bone remodeling activity is evaluated through bone formation markers, such as bone alkaline phosphatase (bAP), osteocalcin and N-terminal of procollagen type I, and bone resorption markers such as CTX.

In postmenopausal osteoporosis, these markers have been shown to have a good correlation with BMD and fracture.²⁷ In a previous study on patients with ISM-related osteoporosis,³ those markers were within the normal range in most of the cases, and there was no correlation with BMD Z score (Fig. 3). The investigators but also other researchers¹² failed to find a predictive value for vertebral fracture of these markers.

Conversely, another study with 45 subjects also involving advSM¹¹ reported increased values of CTX, deoxypyridinoline, bAP, and osteoprotegerin (OPG), although with a wide range of values probably due to the presence of both indolent and aggressive types. In fact, CTX and OPG were higher in patients with advSM rather than ISM and also correlated with serum tryptase.¹¹ Furthermore, a study by van der Veer and colleagues⁵ identified elevated serum CTX levels as a predictive risk factor for fragility fracture and included it in their fracture risk score.

Effectively, in a recent longitudinal study in patients with ISM, the authors found that serum CTX at baseline could predict BMD change, being negatively correlated to BMD change at lumbar spine over the following 30 months (see Fig. 3).²⁸

The correlation between tryptase, BTM, and aggressiveness of SM is in line with the hypothesis of a number-dependent effect of MC on bone metabolism. Of interest is the strong independent correlation in the population of Degboe and colleagues,⁶ between bone marrow tryptase level and fragility fractures; this bone marrow level rather

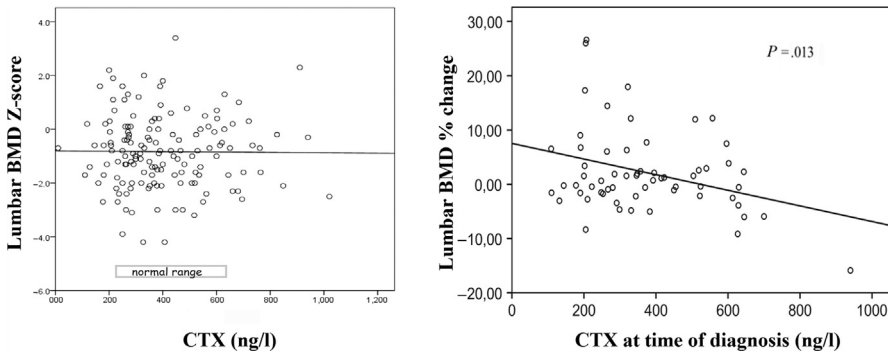


Fig. 3. Relationship between serum CTX and lumbar BMD among patients with ISM, and between baseline CTX and lumbar BMD change over 30 months after diagnosis in nonosteoporotic patients with ISM. (Adapted from Rossini M, Zanotti R, Viapiana O, et al. Bone involvement and osteoporosis in mastocytosis. *Immunol Allergy Clin N Am* 2014;34(2):385; and Artuso A, Caimmi C, Tripi G, et al. Longitudinal evaluation of bone mineral density and bone metabolism markers in patients with indolent systemic mastocytosis without osteoporosis. *Calcif Tissue Int* 2017;100(1):40–6; with permission.)

than the serum level could help to identify patients at higher risk of fracture and recently has also been proposed as a more reliable diagnostic tool.²⁹

On the other hand, there are reports of elevated tryptase levels being associated with greater bone density in patients with SM.³⁰ The authors also observed in their patients with ISM that a positive correlation existed between tryptase levels, Z score BMD, and bAP, thus showing a correlation with bone formation.³¹ In accordance with these data, the authors noticed that patients with diffuse osteosclerosis were characterized by very high tryptase levels and high BTM levels, reflecting the image at bone scintigraphy of a diffuse hyper-uptake (superscan).³ It is known that MC can also stimulate osteoblasts, maybe through tryptase, and osteoblasts can thus increase production of OPG, limiting the activity of osteoclasts.³²

The data reported above give an idea of the complexity of the pathophysiology of bone involvement in SM, with implication of both bone formation and resorption. However, the factors that determine the direction toward the osteoporotic or the osteosclerotic form still remains obscure. It is reasonable to think that the different bone phenotypes are expressions of the relative predominance of one pathway over the others or the presence or absence of permitting or inhibiting cofactors or could also be related to the total number of MC or their activation status, due to aggressiveness of the disease.

There are reports of increased OPG and RANKL in MS. There are reports of MC production of OPG and RANKL production, suggesting a strong role of this pathway in SM bone involvement^{11,33}; as mentioned above, in one of these experiences,¹¹ OPG, BTM, and tryptase were positively correlated.

The canonical Wnt acts, together with bone morphogenetic proteins, predominantly on osteoblasts, to enhance their differentiation and activity, but also it exerts an inhibitory effect on osteoclasts.³⁴

The Wnt system is constitutively activated, and thus, it is regulated by inhibitory modulators; the most known and studied are Dickkopf-1 (Dkk1) and Sclerostin (SOST).³⁴

A German study showed an increase of SOST but not of Dkk1.³³ This datum is coherent with a negative effect on bone formation (with bone turnover imbalance

toward bone loss), even if it is known that SOST increases with age and the SM population was older than controls in that study. In the authors' patients with ISM, the authors failed to find any difference of SOST with matched population, but did find higher Dkk1 serum levels, which correlated with parathyroid hormone, CTX, and bAP.³⁵ However, histomorphometric studies report a higher osteoid presence, higher cellularity, and thus higher Dkk1 seems related more to bone turnover alterations and increased number of osteoblast. Therefore, in the authors' opinion, the pathogenetic role of Wnt pathway is negligible or marginal in SM.^{35,36}

CLINICAL FEATURES

Most of the patients obtain a diagnosis of SM with a delay of years from onset even if most of the time the presenting symptoms leading to diagnosis are the most evident ones, such as skin lesions (eg, maculopapular cutaneous mastocytosis) or anaphylactic reactions.³⁷ The principal clinical bone manifestations are fragility fractures or poorly localized bone pain that is often misdiagnosed because of the rarity of SM. This rarity is probably the reason why among male patients at time of diagnosis, 20% already have multiple vertebral deformities, typically fish-shaped in nature, as seen in GIOP or osteomalacia (Fig. 4). Also to be noted is that the cervical spine can be involved by vertebral fractures, a fact that is quite uncommon in primary osteoporosis.

It is important to highlight that in the Verona ISM cohort, 36% of patients presenting with a history of fractures suffered from nonvertebral ones,³ meaning that cortical bone is also involved, and clinicians should also consider SM in unexplained nonvertebral fractures.

Bone pain is a complaint in 54% of the patients, 18% of which describe it as severe or intolerable.³⁸

Concomitant osteolytic and osteosclerotic lesions are frequent and suggestive of mastocytosis bone involvement.

The clinical meaning of focal bone lesions, especially sclerotic ones, is still uncertain because of the lack of studies on their evolution over time. Similarly, the diffuse osteosclerotic type is usually asymptomatic, and its clinical implication is also still uncertain; in the authors' opinion, it might predispose a more accelerated osteoarthritis.

DIAGNOSIS

Diagnosis in the absence of anaphylactic reaction or skin lesions can be really challenging. Osteoporosis and fragility fractures are common in SM, particularly in men and patients without skin involvement.^{3,5} Osteoporotic fractures are rarely not the only presenting manifestation; thus, it is crucial to investigate this possibility in otherwise unexplained fractures or osteoporosis, especially in men. In patients without typical skin lesions, the flow chart diagnostic algorithm proposed by the authors could be of help (Fig. 5).

In patients diagnosed with SM, it is recommended that a careful screen for bone manifestation be performed.

First, a BMD measurement at lumbar spine and femur (neck and total) by DXA should be obtained and T score and Z score should be considered according to the sex of the patient. However, there is wide variability, and half of the patients have a fragility fracture without a pathologic BMD value.^{3,5} This variability limits the use of DXA as a predictor of fracture, but BMD still remains a key determinant in evaluation.^{5,6} The authors usually perform a DXA scan once a year until stability is achieved and less frequently (between 12 and 24 months) thereafter in osteoporotic patients depending on the case.³⁹ In particular, the authors' data show that patients without

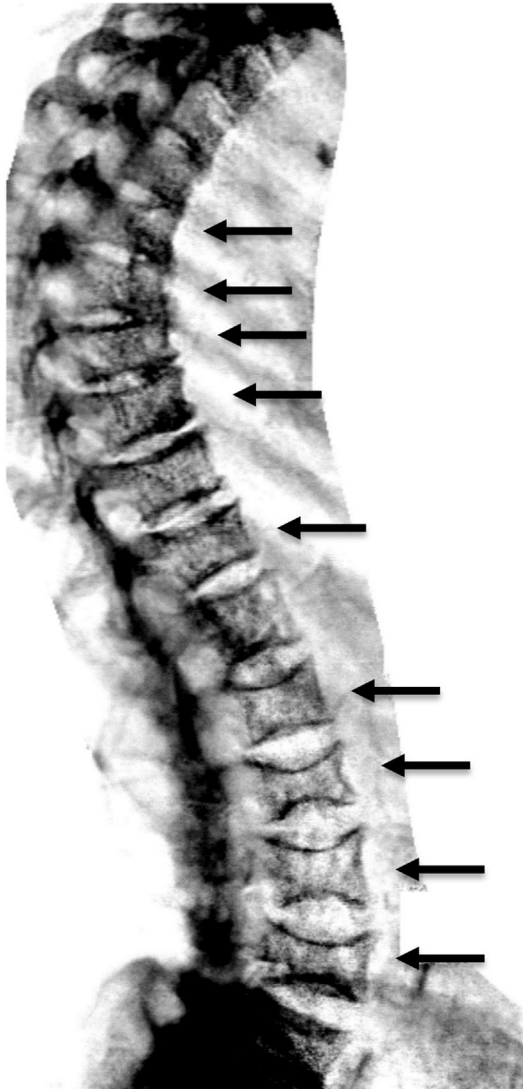


Fig. 4. Vertebral morphometry through DXA showing multiple vertebral fractures (*arrows*).

osteoporosis and with normal serum CTX do not require DXA before an interval of 2 years.²⁸ Thus, in osteopenic patients without particular risk factors and with normal CTX, a DXA evaluation every 24 to 36 months is deemed sufficient.

Because BMD is partially reliable for assessing bone health in SM, a total spine radiography is strongly recommended for early detection of vertebral asymptomatic fractures. A whole skeleton radiograph might be suggested to exclude other focal lytic or sclerotic lesions.

Vertebral fractures should be classified accordingly to the Genant criteria,⁴⁰ because a loss in height greater than 20% with a grade score of 3, based on the entity of height reduction: grade I from 20% to 24%, grade II from 25% to 40%, grade III greater than 40%.

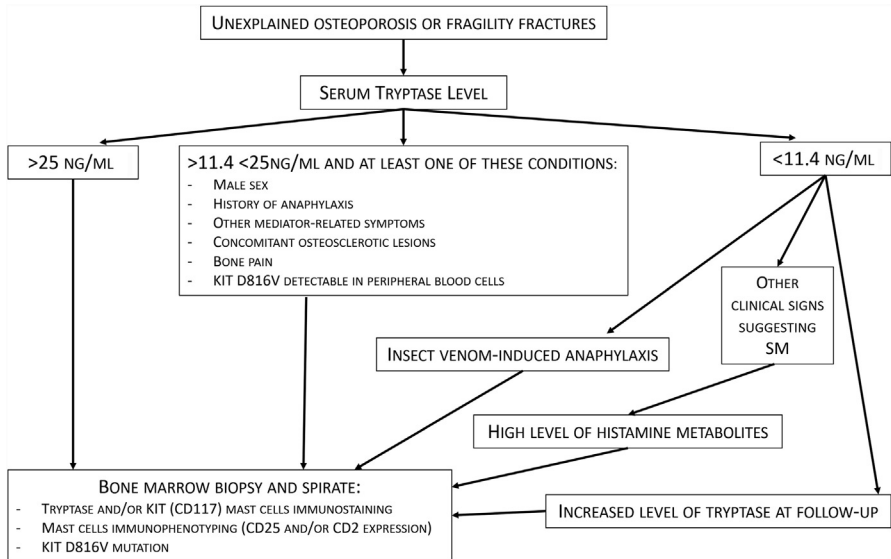


Fig. 5. Diagnostic algorithm to exclude SM in patients with unexplained osteoporosis or fragility fracture but without typical skin lesions. (Adapted from Rossini M, Zanotti R, Orsolini G, et al. Prevalence, pathogenesis, and treatment options for mastocytosis-related osteoporosis. *Osteoporos Int* 2016;27(8):2411–21; with permission.)

DXA technology has recently become very useful in outpatient clinical practice because it combines the possibility of having a BMD measure and a vertebral fractures assessment as well through vertebral morphometry (see Fig. 4), using low radiographs exposition.

In the diagnostic process of unexplained osteoporosis or fractures in the absence of typical skin lesions of mastocytosis, the measurement of serum tryptase seems to be a good screening tool (see Fig. 5), considering that about 95% of patients with SM have above normal serum tryptase levels. It must be said that false positives exist (eg, chronic urticaria, renal insufficiency, other hematologic diseases, Onchocerciasis, ischemic myocardial disease, presence of heterophilic antibodies), and thus, consequently, bone marrow biopsy is mandatory, because it represents the gold standard for diagnosis and the core of diagnostic criteria. Bone marrow biopsy should be considered also in patients with normal tryptase if there are other clinical signs suggesting SM.

Currently, the role of BTM in clinical practice is not clear. Not infrequently the patient with SM with vertebral fractures will have normal BTM, whereas very high BTM serum levels are typically present in diffuse osteosclerosis. In patients with high BTM, a bone scintigraphy could be helpful to detect focal asymptomatic bone lesions and target radiographs examination.⁴¹

The very rare occurrence of large osteolytic lesions leads to the diagnosis of an aggressive SM variant, but if this finding does not correlate with other clinical and laboratory parameters, a histologic evaluation is recommended in order to exclude an associated hematological neoplasm or a solid cancer.⁴²

MANAGEMENT

In patients with ISM, a high prevalence of vitamin D deficiency has been reported²⁸; therefore, the first level of therapy is vitamin D supplementation. The other important

traditional risk factors for osteoporosis and fractures should be taken into consideration and effectively corrected (alcohol consumption, corticosteroids, smoking, calcium intake, and so forth).

Considering the potential pathogenetic role of histamine and other MC mediators, antimediator therapy has been proposed as a therapeutic approach for bone involvement as well⁴³; however, conclusive evidence is still lacking.

The most studied approach for the treatment of mastocytosis-related osteoporosis is the use of antiresorptive drugs, bisphosphonates, with the rationale of preventing bone loss determined by an absolute or relative predominance of osteoclast activity. In particular, different aminobisphosphonates have been used, both oral and parenteral (oral alendronate 70 mg/wk, oral risedronate 35 mg/wk, intra or endovenous pamidronate 90 mg/mo), with a positive effect on lumbar spine BMD but much less on the femoral one.^{4,44–46} Tolerance and adherence to therapy are relevant issues in the general population, and this is even more important in patients with SM that often have gastrointestinal disturbances because of the disease itself. Parenteral administration should then be favored, and the least frequent administration possible would guarantee the best adherence and tolerance. In the authors' experience with ISM, one infusion of zoledronate 5 mg obtained a mean increase in BMD (at both lumbar and femoral sites) double that observed with oral alendronate or pamidronate, along with a reduction of BTM lasting for at least 1 year.⁴⁷ The gain in BMD and suppression of BTM are surrogate markers of anti-fracture efficacy, and therefore, yearly infusions of zoledronate in patients with ISM with nonsevere osteoporosis might be sufficient. However, in patients with previous vertebral fractures, more frequent administration of zoledronate should be recommended.

The authors recently administered denosumab in a few patients refractory or intolerant to bisphosphonates, with the regimen for postmenopausal osteoporosis treatment. The choice was made based on pathophysiologic data on the RANKL/RANK role. In these patients, denosumab was well tolerated and showed positive results on BMD along with a reduction of serum levels of BTM and tryptase.⁴⁸

A rational approach, especially in the presence of low bone formation markers, might be osteoblasts stimulation with teriparatide, the 1 to 34 active fragment of parathyroid hormone. However, no experiences with the use of this anabolic treatment have been reported until now, and the description of an increase in MC in parathyroid bone disease⁴⁹ suggests some safety concerns in SM. In the authors' opinion and based on current knowledge, the use of teriparatide should not be proposed as an alternative approach in the management of mastocytosis-related osteoporosis because this treatment might further enhance the growth and proliferation of abnormal MC and induce more aggressive forms of SM.

In refractory or intolerant patients, the use of cytoreductive drugs has also been suggested as a rescue treatment.⁵⁰ There are studies reporting the use of a combined therapy with interferon- α (IFN- α) and bisphosphonates for cases refractory to bisphosphonates alone.^{39,51–55} This combination appears effective in increasing BMD but is poorly tolerated by the side effects of IFN. Cladribine can be used in patients with SM who are refractory to IFN- α .⁵⁶ Tyrosine kinase inhibitors, such as Midostaurin, are a group of drugs indicated in aggressive forms of SM because they target KIT⁵⁷; currently, there are no data on their effects on BTM, BMD, and fracture risk. There is a case report of one patient with advSM and diffuse osteosclerosis who did not respond to stem cell transplantation but did respond clinically to cytarabine and midostaurin, with resolution of osteosclerosis after midostaurin.⁵⁸

However, in the authors' opinion, more longitudinal data are needed for a better understanding of bone involvement evolution and the impact of treatments in SM.

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