BRIEF OBSERVATION

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Zoledronic Acid in Osteoporosis Secondary to Mastocytosis

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ABSTRACT

BACKGROUND: Osteoporosis is the prevalent manifestation of bone involvement in patients with systemic mastocytosis. Mastocytosis-related osteoporosis is characterized by both absolute and relative prevalence of osteoclastic activity, consistent with the positive results reported in small series of patients with anti-resorptive drugs, such as bisphosphonates. The aim of this study is to investigate the efficacy of zoledronic acid in patients with mastocytosis-related osteoporosis.

METHODS: Twenty-five patients with osteoporosis secondary to indolent systemic mastocytosis were given a single intravenous infusion of 5 mg zoledronic acid dissolved in 100 mL of 0.9% saline over 60 minutes.

RESULTS: After 1 year, the mean increase in bone mineral density was 6.0% ± 4.4% at the spine and 2.4% ± 3.2% at the total hip. Serum levels of bone turnover markers decreased versus baseline: bone alkaline phosphatase −34% and −35%, and C-terminal telopeptide −68% and −56% at 6 and 12 months, respectively. None of the patients reported new fractures during the year of follow-up. In all the first 20 treated patients, a transitory acute phase response was observed, but this was prevented in 4 of 5 subsequent patients in whom acetaminophen was given systematically during the 3 days post-infusion.

CONCLUSIONS: A single 5 mg zoledronic acid intravenous infusion in patients with osteoporosis secondary to indolent systemic mastocytosis is associated with significant increases in spine and hip bone mineral density and decreases of bone turnover markers over at least 1 year. Yearly zoledronic acid might represent a therapeutic option for indolent systemic mastocytosis-associated osteoporosis.

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KEYWORDS: Bisphosphonates; Bone mineral density; Bone turnover markers; Mastocytosis; Osteoporosis; Zoledronic acid

Osteoporosis is the prevalent manifestation of bone involvement in patients with systemic mastocytosis.[1] In a cohort of 75 adult patients with mastocytosis, 31% had osteoporosis and 17% had vertebral fracture.[2] In our experience with the indolent form, predominantly characterized by symptoms related to mast cell degranulation/mediator release or allergies or anaphylaxis, osteoporosis according to the World Health Organization classification (T-score bone mineral density <−2.5) was found in 20% of the patients.[3] Bone mineral density Z-score <−2 was observed in 9% of the female patients and 28% of the male patients.[3] In a study in patients with indolent systemic mastocytosis, urinary methylhistamine was a significant age- and gender-adjusted predictor of osteoporosis.[4]

Mastocytosis-related bone loss seems to be driven by increased osteoclastic bone resorption secondary to release by mast cells of histamine, tryptase, heparin, or proinflammatory or resorptive cytokines (eg, interleukin-1, interleukin-6, and tumor necrosis factor-alpha),[5] and then of receptor activator of nuclear factor kappa-B ligand activity.[6,7] However, osteoporosis is not observed in most patients, and radiographic features of osteopetrosis have been reported in a small proportion.[1,3] Thus, it was hypothesized that increased osteoclastic activity may be associated with

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changes in bone formation ranging from inappropriate to exceeding bone resorption.[3] These large changes in bone formation might be related to the activity of the Wingless signaling pathway.[7,8] In patients with osteoporosis, the histomorphometric analysis revealed an increased number of both osteoclasts and osteoblasts,[9] together with deterioration of trabecular bone structure, and serum bone turnover markers were reported normal or increased.[1,3,7,10] Overall, these results indicate that when osteoporosis occurs in indolent systemic mastocytosis, this is characterized by the prevailing of osteoclastic activity, which provides a rationale for the use of antiresorptive drugs such as bisphosphonates. We report our experience in 25 patients with indolent systemic mastocytosis-related osteoporosis treated with a single infusion of zoledronic acid.

CLINICAL SIGNIFICANCE

- In patients with osteoporosis secondary to indolent systemic mastocytosis, 5 mg of zoledronic acid administered in an intravenous infusion is associated with significant decreases of bone turnover markers and bone mineral density increases for at least 1 year.
- Zoledronic acid represents a therapeutic option for the treatment of osteoporosis secondary to indolent systemic mastocytosis.

PATIENTS AND METHODS

Patients

Twenty-five patients affected by indolent systemic mastocytosis (13 men and 12 postmenopausal women, with a mean age of 58 ± 10 [standard deviation{SD}] years; range, 43-84 years) with osteoporosis according to the World Health Organization criteria (lumbar spine or hip bone mineral density T-score ≤2.5 SD or fragility fractures) were studied. Mastocytosis was proven by bone marrow biopsy, showing mast cell infiltrates expressing CD117, CD2, and C25. Other causes of osteoporosis were excluded.

Methods

Biochemical assessment included serum calcium, phosphorus, 25-hydroxy vitamin D, parathyroid hormone, bone alkaline phosphatase, serum C-terminal collagen telopeptide, serum tryptase, and a search for D816V KIT mutations in bone marrow specimens. Baseline spine x-ray was obtained. Bone mineral density was measured by dual-energy x-ray absorptiometry (Hologic QDR Delphi; Hologic Inc, Bedford, MA) at the lumbar spine (L1-L4) and the proximal hip. Fractured vertebrae were not included in the analysis, and in 4 patients severe spine deformities prevented any measurement. All

Table 1 Clinical, Densitometric, and Laboratory Characteristics of Patients Before Treatment

Patients	Age (y)	Fractures	Spinal T-score	Spinal Z-score	Neck T-score	Neck Z-score	Total Hip T-score	Total Hip Z-score	CTX ng/mL	bALP U/L	PTH pg/mL
1 F	84	L1	—	—	−1.2	1.1	−1.4	1.2	0.371	10	6
2 M	43	—	−2.4	−2	−2.5	−1.8	−1.8	−1.4	0.508	14	6.3
3 F	58	—	−3	−2	−1.8	−0.8	−1	−0.4	0.466	14	6.3
4 M	65	T6	−4.4	−3.8	−1.5	−0.5	−1.5	−1	0.491	16	5.6
5 M	45	T7	−3.1	−3	−2.7	−2.2	−1.9	−1.7	0.612	13	2.8
6 M	58	T12, L1	−2	−1.5	−0.5	0.4	−0.5	−0.1	0.413	11	7.6
7 F	54	—	−2.6	−1.3	−2.7	−1.8	−1.2	−0.7	0.34	22	4.1
8 F	56	—	−3.4	−2.4	−2.8	−1.8	−1.9	−1.1	0.562	15	5.5
9 M	48	T7	−1.9	−1.7	−2.5	−1.9	−1.3	−1.1	0.509	24	7.7
10 F	58	—	−2.8	−0.9	−1.7	−0.3	−1.4	−0.2	0.385	24	8.2
11 F	56	T7	−2.2	−1	−2	0.9	−0.9	−0.3	0.5	17	4.3
12 M	63	T9	−2.3	−2.4	−2.6	−1.9	−2.3	−2.1	0.65	14	7.7
13 M	48	T8	−4	−3.9	−1.7	−1.2	−1.7	−1.4	0.25	10	2.9
14 M	60	—	−3.1	−2.5	0	−0.4	−0.4	0	0.489	12	6.4
15 M	46	L4	−1.3	−1.2	−0.2	0.3	0.6	0.8	0.625	25	4.7
16 M	71	T7, L3, L4	—	—	−2.1	−0.9	−0.4	0.2	0.312	19	7.6
17 F	47	—	−3.2	−2.8	−1.7	−1.6	−1.6	−1.6	0.49	18	5.2
18 F	61	—	−3.1	−1.6	−2.3	1.2	−1.9	−1.1	0.764	15	5.9
19 F	75	—	—	—	−3.2	−1.3	−2.5	−0.8	0.346	11	8.3
20 M	56	T7, T8	−2.1	−1.9	−1.5	−0.7	−1.1	−0.7	0.683	8	4.8
21 F	60	L1, L4, L5	—	—	−1.7	−0.5	−1.4	−0.6	0.712	21	7.2
22 F	55	—	−3.5	−2.9	−1.7	−0.9	−0.4	0.1	0.614	15	6
23 M	59	T8	−2	−1.8	−1.2	−0.4	−1	−0.6	0.3	12	8
24 M	49	—	−2.7	−2.5	−1.2	−0.6	−1	−0.8	0.23	19	3.5
25 F	74	—	−2.5	−0.7	−1.7	−0.2	−0.6	0.6	0.58	13	8.7

bALP = bone alkaline phosphatase; CTX = C-terminal telopeptide; F = female; M = male; PTH = parathyroid hormone.