Predictors of new fragility fractures after diagnosis of indolent systemic mastocytosis

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Background: Fragility fractures (FFxs) and osteoporosis occur frequently in patients with indolent systemic mastocytosis (ISM), even before 50 years of age.

Objective: We sought to develop a prediction model to identify individual patients with ISM at risk of new FFxs.

Methods: Data on lifetime fractures and trauma circumstances were collected from vertebral morphometry, patients' records, and questionnaires. Clinical, lifestyle, and bone characteristics were measured. Patients receiving treatment for osteoporosis before ISM diagnosis or with missing bone data were excluded from FFx risk assessment.

Results: In total, 389 lifetime fractures occurred in 127 of the 221 patients with ISM (age, 19-77 years), including 90 patients with 264 FFxs. Median follow-up after diagnosis was 5.4 years (range, 0.4-15.3 years), with 5- and 10-year FFx risks of 23% ± 3% and 31% ± 4%, respectively. Male sex, high levels of bone resorption (serum type I collagen C-telopeptide), low hip bone mineral density, absence of urticaria pigmentosa, and alcohol intake at the time of ISM diagnosis were independent predictors of future FFxs. The MastFx score, a prediction model using these 5 characteristics, showed good accuracy (area under the curve, 0.80) to determine the risk of new FFxs. QFracture, a validated risk scoring tool for persons aged 30 to 99 years, was not useful in patients with ISM.

Conclusion: The MastFx score distinguishes patients with ISM at high, intermediate, and low risk of new FFxs. The included characteristics sex, serum type I collagen C-telopeptide, hip bone mineral density, urticaria pigmentosa, and alcohol intake are easy to collect in clinical practice. The high occurrence of FFxs in patients with ISM underlines the importance of optimizing bone quality and early start of therapeutic prevention in patients at risk. (J Allergy Clin Immunol 2014;134:1413-21.)

Key words: *Systemic mastocytosis, fragility fractures, fracture risk scoring tool, bone turnover markers, bone mineral density, alcohol, sex, urticaria pigmentosa, serum type I collagen C-telopeptide*

Abbreviations used

AUC: Area under the curve
BMD: Bone mineral density
BMI: Body mass index
BTM: Bone turnover marker
CV_{inter}: Interassay coefficient of variation
FFx: Fragility fracture
FRAX: Fracture Risk Assessment Tool
HR: Hazard ratio
ISM: Indolent systemic mastocytosis
MH: Methylhistamine
MIMA: Methylimidazole acetic acid
ROC: Receiver operating characteristic
sCTX: Serum type I collagen C-telopeptide
UP: Urticaria pigmentosa

Indolent systemic mastocytosis (ISM) is defined by the presence of abnormal mast cells outside the skin, principally in the bone marrow.[1] Mast cells produce and release a large number of different mediators, such as histamine, prostaglandin D_2, platelet-activating factor, proinflammatory cytokines, leukotrienes C_4 and D_4, chemokines, and tryptase.[2] Symptoms and signs are caused by release of these mast cell mediators, local accumulation of mast cells, or both. Manifestations vary strongly in nature and severity and can include skin and gastrointestinal symptoms, anaphylaxis, musculoskeletal pain, and neuropsychiatric symptoms.

Fragility fractures (FFxs), osteoporosis, or both occur in approximately half of the patients with ISM.[3-9] Notably, the prevalence of FFxs was high in men, even in those less than 50 years of age.[4] Mast cell mediators are branded to have deleterious effects on bone metabolism.[10,11] In addition, activated mast cells release the proinflammatory cytokines IL-1, IL-6, and TNF-α,[12] which are important regulators of bone resorption.[10] Some patients with ISM exhibit increased serum IL-6 levels, and a correlation with disease severity was found in a group of patients with different types of mastocytosis.[13,14] Furthermore, alcohol triggers mast cell degranulation.[15-17] Its intake can be associated with a number of adverse reactions in patients with ISM. Apart from toxicological effects, intolerance occurs and might manifest clinically as flushing and, in rare cases, as generalized urticaria and anaphylactic reactions after ingestion.

In the general population multiple tools have been developed to assess a patient's fracture risk based on models that integrate age and sex with additional risk factors (eg, low body mass index [BMI], previous FFxs, underlying diseases, use of corticosteroids, smoking, and excessive alcohol intake), with or without the use of bone mineral density (BMD) at the femoral neck. Recently, the National Institute of Clinical Excellence's guidelines

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recommended assessing bone health by using one of the 2 validated scoring systems, namely the Fracture Risk Assessment Tool (FRAX) and QFracture.[18] However, these fracture risk scoring systems do not take into account specific risk factors associated with FFxs in the younger population. FRAX is limited to persons older than 40 years. Even though QFracture includes persons between 30 and 40 years of age, the score is less reliable because the number of fractures in the data set is small for this age group. In addition, the prevalence of multiple fractures in patients with ISM[3,4] is much higher than the prevalence found in European population studies.[19-23] Therefore the aim of the present study was to investigate the predictive value of certain patient characteristics at the time of diagnosis for the occurrence of future FFxs in patients with ISM. By using these characteristics, an easy-to-use prediction model, named the MastFx score, was developed and tested to identify patients with ISM at risk of new FFxs.

METHODS

Study population

Between 1981 and August 2012, ISM was diagnosed in 228 consecutive patients at the referral centre for mastocytosis of the University Medical Center Groningen. The diagnosis was established by fulfilling the criteria of the World Health Organization Classification of Mastocytosis. Patients with aggressive forms of systemic mastocytosis were excluded. Smoldering systemic mastocytosis, a provisional subentity of ISM with detectable B findings (criteria used for classification of systemic mastocytosis) caused by the mast cell disease process, was excluded as well.[24]

Fracture data were collected from medical records and lateral radiographs of the thoracolumbar spine combined with a questionnaire sent to all patients. FFxs, also known as low-level (or "low-energy") trauma fractures, were defined as fractures that result from mechanical forces that would not ordinarily result in fractures.[25] In cases in which it was not possible to discriminate between high- or low-energy trauma circumstances, a telephone call was made to clarify. Fracture data of 7 (3%) of the 228 patients could not be retrieved, and these patients were excluded.

BMD of the lumbar spine (anterior-posterior projection at L1-L4) and hip (total proximal femur) were measured with dual energy x-ray absorptiometry (DXA) (Hologic QDR Discovery, Waltham, Mass). BMD *T*-scores were calculated by using the National Health and Nutrition Examination Survey reference database. Osteoporosis was defined according to World Health Organization guidelines as a BMD *T*-score of −2.5 or less, and osteopenia was defined as a BMD *T*-score of between −1.0 and −2.5.

In addition, data regarding osteosclerosis, the presence of urticaria pigmentosa (UP), and anaphylaxis were collected (definitions, details, or both were published previously[4]). For the predictor analysis, 40 of the 221 patients were excluded because of treatment for osteoporosis (eg, bisphosphonates or parathyroid hormone) before ISM diagnosis (n = 28), sex change (n = 1), fracture or surgery within the last 6 months before diagnosis (n = 2), or missing BMD and bone turnover marker (BTM) data (n = 9, Fig 1). The Medical Ethical Review Board of the University Medical Center Groningen declared that the study was performed in accordance with regulations of the review board for publication of subjects' data.

Biochemical markers

BTM was studied by means of assessment of the formation markers bone-specific alkaline phosphatase, procollagen type 1 N-terminal peptide, and osteocalcin and the resorption marker serum type I collagen C-telopeptide (sCTX).[26] Bone-specific alkaline phosphatase levels were measured by using ELISA (Metra Biosystems, Mountain View, Calif; interassay coefficient of variation [CV_{inter}], 5.5%), procollagen type 1 N-terminal peptide levels were measured by using an RIA (Orion Diagnostica, Espoo, Finland; CV_{inter}, 9.0%), osteocalcin levels were measured by using an immunoradiometric assay (BioSource Europe S.A, Nivelles, Belgium; CV_{inter}, 9.4%), and sCTX levels were measured by using an electrochemiluminescence immunoassay (Elecsys 2010; Roche, Mannheim, Germany; CV_{inter}, 10.8%). Serum samples were stored within 1 hour after venipuncture at −20°C until analysis. BTM *Z*-scores, the number of SDs from the normal mean corrected for age and sex, were calculated by using a Dutch reference group (200 men and 350 women) checked for serum 25-hydroxyvitamin D levels of greater than 50 nmol/L, as well as for the absence of osteoporosis (BMD *T*-score, >−2.5) after 50 years of age. *Z*-scores were calculated as follows:

(BTM value of individual patient − Mean BTM value of matched 10-year cohort of healthy reference group)/SD of this matched reference cohort.

Tryptase levels were determined by using the B12 assay (Pharmacia UniCAP Tryptase; Thermo Fisher Scientific/Pharmacia and Upjohn, Uppsala, Sweden; CV_{inter}, 5.8%).[27] Reference values for healthy subjects are from Pharmacia and Upjohn, showing a geometric mean level of 3.8 μg/L and an upper 95th percentile of 11.4 μg/L. Urine samples were collected after an overnight fast, discarding the first voiding after wakening, to measure methylhistamine (MH) and methylimidazole acetic acid (MIMA) values. For 24 hours before urine collection, patients were asked to refrain from histamine-rich foods and drinks, such as sauerkraut, canned fish, yogurt, and wine. The MH value was determined by using an isotope-dilution mass fragmentographic method.[28] MIMA was determined as described previously,[29] with some modifications using isotope dilution mass fragmentography. For MH and MIMA excretion, mean ± SD values of an apparently healthy population were 101 ± 33 μmol/mol (range, 50-154 μmol/mol; CV_{inter}, 6.8%) and 1.3 ± 0.3 mmol/mol (range, 0.9-1.9 mmol/mol; CV_{inter}, 4.2%) creatinine, respectively.[30]

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics 20 software (SPSS, Chicago, Ill). Results were expressed as means ± SDs or medians (ranges) for parametric and nonparametric data, respectively. Predictor analysis for the occurrence of FFxs was performed by using univariate and multivariate Cox regression with backward Wald inclusion of variables with a *P* value of .20 or less in univariate analysis. The *P* value for stepwise removal was .10, and *P* values of less than .05 were considered statistically significant. For continuous variables with significant outcomes in univariate analysis, relevant cutoff points were determined according to clinical applicability and checked by using receiver operating characteristic (ROC) curves. These categorized variables were used in multivariate analysis. The final prediction model, named the MastFx score, was obtained by rounding the regression coefficients of the multivariate model. ROC analysis was used to determine the performance of this prediction model (area under the curve [AUC] < 0.70 was interpreted as poor, 0.70 < AUC < 0.80 was interpreted as moderate, 0.80 < AUC < 0.90 was interpreted as good, and AUC > 0.90 was interpreted as high accuracy). Finally, the MastFx scores were compared with risk scores calculated with one of the National Institute of Clinical Excellence–recommended validated scoring tools, the QFracture-2012 algorithm (version 1.0; ClinRisk Ltd, Leeds, United Kingdom). For patients with ISM aged less than 30 years (n = 22), the QFracture risk was calculated with an age of 30 years.

RESULTS

FFxs

Information about lifetime fractures was retrieved for 221 (97%) patients. In total, 389 lifetime fractures occurred in 127 patients. Of these fractures, 125 were high-energy trauma fractures, and 264 were FFxs. Before the ISM diagnosis was made, 54 patients reported 139 FFxs. After the ISM diagnosis, 56 patients reported 125 new FFxs during a median follow-up of 5.4 years (range, 0.4-15.3 years; Fig 2, *A*), with a 5- and 10-year fracture-free survival of 77% ± 3% and 69% ± 4%, respectively.

Forty patients were excluded from the predictor analysis to avoid bias of factors influencing fracture risk, BMD, and/or BTM (Fig 1). In the remaining 181 patients with ISM, 27 reported 40