Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors

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Clinical phenotype in systemic mastocytosis (SM) is markedly variable, which complicates prognostication and decision making regarding the choice and timing of therapy. In a retrospective study of 342 consecutive adult patients with SM seen at the Mayo Clinic between 1976 and 2007, disease subdesignation according to the World Health Organization (WHO) proposal was indolent (ISM) in 159 (46%), with associated clonal hematologic non–mast cell lineage disease (SM-AHNMD) in 138 (40%), aggressive (ASM) in 41 (12%), and mast cell leukemia in 4 (1%). *KIT*D816V was detected in bone marrow–derived DNA by allele-specific polymerase chain reaction (PCR) in 68% of 165 patients evaluated (ISM, 78%; ASM, 82%; SM-AHNMD, 60%; *P* = .03); *JAK2*V617F was detected in 4%, all in SM-AHNMD. Compared with those with nonindolent SM, life expectancy in ISM was superior and not significantly different from that of the age- and sex-matched US population. In addition, multivariable analysis identified advanced age, weight loss, anemia, thrombocytopenia, hypoalbuminemia, and excess bone marrow blasts as independent adverse prognostic factors for survival. The current study validates the prognostic relevance of the WHO subclassification of SM and provides additional information of value in terms of both risk stratification and interpretation of clinical presentation and laboratory results. (Blood. 2009;113:5727-5736)

Introduction

Mastocytosis is a heterogeneous disorder characterized by the abnormal growth and accumulation of morphologically and immunophenotypically abnormal mast cells (MCs) in one or more organs. The clinical presentation of mastocytosis is diverse, and many patients do not fit the classical description—namely, a variably long history of urticaria pigmentosa (UP), followed by the insidious onset of flushing, cramping abdominal pain, diarrhea, bone pain, and hepatosplenomegaly.[1-4] Unlike pediatric cases, most adults with UP-like skin lesions have systemic disease (ie, systemic mastocytosis [SM]) at presentation, a condition generally confirmed by a bone marrow (BM) biopsy.[5] MCs are derived from $CD34^+/KIT^+$ pluripotent hematopoietic cells in the bone marrow[6]; its neoplastic counterparts are morphologically atypical (spindled shape, hypogranular cytoplasm, nuclear atypia),[7,8] and express abnormal cell surface markers (CD25 and/or CD2).[9,10] Most, if not all, adult mastocytosis patients carry gain-of-function KIT receptor mutations, most commonly D816V in the tyrosine kinase domain.[11,12]

The natural history of SM, ranging from indolent forms spanning years to more aggressive subtypes that rapidly progress to leukemia, complicates decision making regarding the choice of therapeutic modalities and timing of intervention. In 1988, Mayo Clinic investigators proposed a classification wherein SM patients were grouped into the following subtypes: (1) indolent SM (ISM); (2) SM with associated hematologic disorders (SM-AHD); (3) aggressive SM (ASM); and (4) mast cell leukemia (MCL), based on distinct clinicopathologic features.[2] In 2001, the World Health Organization (WHO) formalized this classification and further refined it by incorporating recent advances in SM, including identification of *KIT*D816V, aberrant expression of cell surface markers on neoplastic MCs, and elevated tryptase level in serum.[13] Although the WHO proposal represents a major advance in identifying clinically distinct SM subgroups based on defined criteria and, consequently, has been widely adopted in clinical practice, it has hitherto not been validated in a large cohort of SM patients.

The aim of the current study was (1) to describe the clinical and laboratory features at presentation in a large cohort of SM patients; (2) to describe the risk of leukemic transformation and estimate mortality of SM patients within the context of the current WHO classification; (3) to estimate life expectancy relative to age- and sex-matched controls as a basis for clinical decision making; (4) to evaluate prognostic relevance of the WHO subclassification of SM, and to identify additional clinical, laboratory, and/or bone marrow histologic features that have prognostic value; and (5) to evaluate the prevalence and prognostic relevance of *KIT*D816V and *JAK2*V617F mutations in this cohort.

Methods

Patients

The current study was approved by the Mayo Clinic Institutional Review Board. All patients provided informed authorization for use of their medical records for research purposes, and research was carried out in accordance with the principles of the Declaration of Helsinki. Prospective SM patients

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18 years of age or older were identified by querying institutional electronic databases from January 1976 to October 2007. The flagged medical charts were thoroughly reviewed; study inclusion patients were required to have BM pathology reviewed at our institution and presence of SM confirmed. Clinical and laboratory features at diagnosis, survival data, and progression to leukemia were documented, and SM was subclassified according to the 2001 WHO proposal.[14]

Bone marrow studies

BM aspirates and trephine sections were reviewed by one of us (C.-Y.L.). All patients satisfied the 2001 WHO criteria for the diagnosis of SM. Special immunohistochemical stains were used to identify MC in biopsy material, including tryptase (n = 228; 67%) and KIT (n = 123; 36%). The other stains used were Giemsa, toluidine blue, chloroacetate esterase, aminocaproate esterase, and acridine orange. Pathognomonic MC infiltrates were confirmed and overall BM cellularity and MC burden were recorded for each case. The percentage BM involvement by MC was based on review of trephine specimens. The pattern of MC infiltration, percentage of BM blasts in aspirate smears, and degree of eosinophilic infiltration were also recorded. CD2 and/or CD25 expression on BM MCs was studied by immunohistochemistry and/or flow cytometry in a subset of cases (n = 84; 25%), as previously described.[10] Cytogenetic analysis was performed at diagnosis and the karyotype was classified using the International System for Cytogenetic Nomenclature Criteria.

Molecular studies

Mutation analysis was performed in DNA derived from archived cytogenetic pellets obtained at the time of BM biopsy. *KIT*D816V was evaluated using an allele-specific oligonucleotide polymerase chain reaction assay with fragment analysis performed on an ABI 3130xl genetic analyzer (Applied Bioscience, Foster City, CA). Briefly, polymerase chain reaction (PCR) was used to amplify a fragment containing the mutation site in 2 separate tubes: one containing a reverse primer complementary to the unmutated sequence and the other containing a reverse primer complementary to the mutated sequence. Each reverse primer was labeled with a fluorescent tag and both tubes contained an identical, nonlabeled forward primer. Both primer sets amplified a 200-bp fragment that differed only at the mutation site. Samples negative for mutation lacked an amplified fragment in the mutated reaction tube, whereas positive samples showed amplified fragments in both the unmutated and mutated tubes. The test is sensitive to 0.01% as determined by dilution of DNA from a positive cell line (HMC-1, containing homozygous mutation) in DNA from a negative cell line (HL-60). The primer sequences were as follows: forward primer: 5′-AATATAAGCAACACTATAGT-3′; reverse primer unmutated: 5′-FAM-ATTAGAATCATTCTTGATGA-3′; reverse primer mutated: 5′-HEX-ATTAGAATCATTCTTGATGT-3′. PCRs were performed in a total volume of 25 μL using approximately 50 ng DNA, 20 pmol each primer, 5 nmol dNTPs, 1.75 units AmpliTaq-Gold, and standard PCR buffer (1.5 mM $MgCl_2$, 10 mM Tris-HCl, pH 8.3, 50 mM KCl). *JAK2*V617F analysis was performed as previously described.[15]

Statistical analyses

Actuarial probability of survival and leukemia-free survival were estimated using the Kaplan-Meier product limit method. Overall survival was defined as the time between diagnosis and death (as a result of all causes) or end of follow-up (censored observations). Leukemia-free survival was calculated from diagnosis to progression to acute leukemia/MCL or end of follow-up. Comparison between Kaplan-Meier curves was carried out by the log-rank test. Univariate and multivariate analyses were performed by Cox proportional hazards regression model. Expected survival curves were calculated using Hakulinen cohort method and were matched by age and sex to the US population for the appropriate time period based on diagnosis date.[16-18] The Fisher exact test or χ^2 test for 2×2 contingency tables and Wilcoxon rank-sum test or Kruskal-Wallis test were used to test for differences in proportions of nominal variables and medians of continuous variables, respectively. Correlation between 2 continuous variables was determined with the nonparametric Spearman rank-order correlation coefficient. Statistical analyses of the data were carried out using the StatView software package (SAS version 9.1; SAS Institute, Cary, NC).

Table 1. Demographic and clinical characteristics at referral of 342 patients with SM

Characteristic	No. of patients (%)	Median (range)
Total no. of SM patients	342	
ISM	159 (46)	
Isolated bone marrow mastocytosis	36 (23)	
Smoldering systemic mastocytosis	22 (14)	
ASM	41 (12)	
SM-AHNMD	138 (40)	
MCL	4 (1)	
Male	188 (55)	
Age, y		57 (19-87)
Time from appearance of symptoms to diagnosis of SM, mo		33 (0-516)
Follow-up, mo		
From onset of symptoms		69 (1.6-741.1)
From diagnosis of SM		20.7 (0-417.1)
Clinical findings		
Urticaria pigmentosa	140 (41)	
Cutaneous symptoms*	182 (53)	
Constitutional symptoms†	142 (42)	
Mediator-related symptoms‡	160 (47)	
Idiopathic and/or recurrent anaphylactoid reaction	57 (17)	
Musculoskeletal symptoms§	107 (31)	
Gastrointestinal symptoms‖	221 (65)	
Hepatosplenomegaly		
Hepatomegaly, n = 342	92 (27)	
Splenomegaly, n = 335	123 (37)	
Both hepatomegaly and splenomegaly, n = 335	72 (21)	
Lymphadenopathy¶	73 (21)	
Leukemic transformation (AML or MCL)	21 (6)	

ISM indicates indolent systemic mastocytosis (SM); ASM, aggressive SM; SM-AHNMD, SM with associated clonal hematologic non–mast cell lineage disease; MCL, mast cell leukemia; AML, acute myeloid leukemia; and No., number.

*Includes pruritus, flushing, urticaria, and angioedema.

†Includes weight loss, fever, chills, and night sweats.

‡Includes headache, dizziness/lightheadedness, syncope/presyncope, hypotension, anaphylaxis, palpitation/tachycardia, bronchoconstriction/wheezing, and peptic ulcer disease.

§Includes bone pain, arthralgias, and myalgias.

‖Includes nausea/vomiting, dyspepsia, dysphagia, diarrhea, constipation, abdominal pain/cramping, bloating/flatulence, early satiety, heartburn, gastrointestinal tract bleeding, malabsorption, and steatorrhea.

¶Either palpable or detected by imaging studies.

Results

Clinical and laboratory features

The demographic, clinical, and laboratory features of the 342 study patients are summarized in Tables 1 and 2 and compared between WHO SM subgroups in Table 3. One hundred fifty-nine patients (46%) had ISM; 138 (40%), SM-AHNMD; 41 (12%), ASM; and 4 (1%), MCL. One patient each with SM-AHNMD and MCL presented with a histologically confirmed focal mast cell sarcoma-like lesion (iliac bone and chest wall, respectively). A greaterproportion of SM-AHNMD patients were male compared with ISM and ASM ($P < .001$). ISM patients were younger ($P < .001$) and exhibited a longer duration of symptoms before diagnosis ($P < .001$)

Table 2. Laboratory findings at referral of 342 patients with SM

Laboratory	No. of patients (%)	Median (range)
Hemoglobin, g/L	341 (99)	128 (51-174)
Hb < 100	64 (19)	90 (51-99)
White blood cell count, $\times 10^9$/L	340 (99)	7.6 (1.2-87.2)
WBC > 10	109 (32)	15.4 (10.1-87.2)
WBC 4-10	198 (58)	6.6 (4.1-10)
Absolute neutrophil count, $\times 10^9$/L	333 (97)	4.3 (0.2-42.5)
Absolute monocyte count, $\times 10^9$/L	333 (97)	0.4 (0-81)
Absolute lymphocyte count, $\times 10^9$/L	333 (97)	1.9 (0-15.8)
Absolute eosinophil count, $\times 10^9$/L	332 (97)	0.2 (0-38.4)
AEC 1.5 or more	49 (15)	3.8 (1.5-38.4)
Platelet count, $\times 10^9$/L	334 (98)	212 (2-1625)
PLT > 100	269 (81)	248 (101-1625)
PLT 50-100	39 (12)	73 (54-97)
PLT < 50	26 (8)	28 (2-46)
Albumin, 35-50 g/L	265 (77)	39 (20-51)
Albumin < 35	51 (19)	31 (20-34)
Total protein, 63-79 g/L	265 (77)	72 (47-94)
TP WNL	210 (79)	72 (63-79)
Serum alkaline phosphatase, 45-115 U/L	318 (93)	181 (19-3680)
SAP > UNL	127 (40)	395 (111-3680)
Aspartate aminotransferase, 8-48 U/L	320 (94)	18 (1-194)
AST > UNL	37 (12)	46 (32-194)
Alanine aminotransferase, 7-55 U/L	99 (29)	20 (4-222)
ALT > UNL	10 (10)	82 (47-222)
Total bilirubin, 1.71-17.1 μM	292 (85)	12 (1.71-133.4)
T bili > UNL	65 (22)	25.7 (18.8-133.4)
Lactate dehydrogenase, 122-222 U/L	164 (48)	150.5 (11-926)
LDH > UNL	28 (17)	324.5 (213-926)
Ferritin, 20-300 μg/L	105 (31)	215.9 (6-17 980)
Ferritin > UNL	47 (45)	658 (207-17 980)
Serum tryptase, < 11.5 ng/mL	160 (47)	63.6 (3.7-2000)
Tryptase 11.5 or more	154 (96)	66.6 (11.9-2000)
Tryptase 200 or more	33 (21)	303 (200-2000)
Urine histamine, < 35 μg/g Cr/24h	58 (17)	62.3 (12-985.6)
U histamine 35 or more	41 (71)	107.6 (36.7-985.6)
Urine *N*-methylhistamine, 30-200 μg/g Cr	64 (19)	354.5 (5-5447)
U M-histamine > UNL	52 (81)	508.5 (98-5447)
Urine beta prostaglandin F2α, 1000 ng or less/24 h	99 (29)	2215 (119-21 608)
U PGF2α > UNL	74 (75)	3262 (1132-21 608)

g indicates grams; dL, deciliter; L, liter; UNL upper normal limit; WNL, within normal limits; U, units; μg, micrograms; mg, milligrams; ng, nanograms; Cr, creatinine; and No., number.

compared with the other WHO subgroups. ISM patients also exhibited a higher prevalence of UP-like skin lesions ($P < .001$), cutaneous symptoms ($P < .001$), MC mediator-related symptoms ($P < .001$), anaphylactoid reactions ($P < .001$), and gastrointestinal symptoms ($P = .05$). In contrast, patients with ASM and SM-AHNMD exhibited a greater frequency of constitutional symptoms ($P < .001$), hepatosplenomegaly ($P < .001$), and lymphadenopathy ($P = .005$).

Approximately one-third and one-quarter of SM-AHNMD and ASM patients, respectively, had significant anemia (Hgb < 100 g/L [10 g/dL]) and thrombocytopenia (platelets $< 100 \times 10^9$/L), and 51% of SM-AHNMD patients exhibited leukocytosis ($P < .001$). Fifty-six (16%) patients exhibited prominent eosinophilia (absolute eosinophil count $> 1.5 \times 10^9$/L [1500/μL]): 31% and 22% with SM-AHNMD and ASM, respectively, versus 3% with ISM ($P < .001$). Relatively few ISM patients exhibited increased levels of serum uric acid (3%), lactate dehydrogenase (4%), bilirubin (11%), or ferritin (18%); or hypoalbuminemia (9%)—in contrast, a 2- to 3-fold greater proportion of SM-AHNMD and ASM patients displayed these laboratory abnormalities ($P \leq .004$). Serum tryptase (normal < 11.5 ng/mL) was measured in 160 patients (47%), and virtually all (96%) had an elevated level (median 64 ng/mL; range 4 to 2000 ng/mL). A greater proportion of ASM and SM-AHNMD patients exhibited a serum tryptase level 200 ng/mL or higher compared with ISM patients ($P = .009$).

Bone marrow histology

Bone marrow histopathologic findings are described in Table 4. The median BM cellularity for the ISM, ASM, SM-AHNMD, and MCL subgroups was 50% (range 20%-100%), 75%, (30%-100%) 90%, (30%-100%), and 88%, (80%-95%), respectively ($P < .001$). The median BM MC percentage for the whole group of patients was 10% (range 1%-90%) and was significantly ($P = .003$) higher in MCL (median, 75%; range, 60%-90%) compared with ASM (median, 13%; range, 1%-70%), SM-AHNMD (median, 11%; range, 1%-70%), or ISM (median, 10%; range, 1%-90%). All 27 patients with BM blasts 5% or more were diagnosed with SM-AHNMD (9 had refractory anemia with excess blasts-2 [RAEB-2]; 7, chronic myelomonocytic leukemia-1 [CMML-1]; 4, myeloproliferative neoplasm (MPN)-unclassifiable; 2, RAEB-1; 2, AML-M2; 1, CMML-2; 1, chronic eosinophilic leukemia; and 1, essential thrombocythemia).

Table 3. Comparison of demographic, clinical, and laboratory characteristics between SM subgroups

Characteristic	No. (%) of patients	Median (range)	ISM	ASM	SM-AHNMD	*P* for ISM vs ASM	*P* for ASM vs AHNMD	*P* for ISM vs AHNMD	Overall *P*
Total no. of SM	342		159 (46)	41 (12)	138 (40)				
Demographic characteristics									
Male	188 (55)		69 (43)	19 (46)	97 (70)	NS	.005	< .001	< .001
Age, y		57 (19-87)	49 (19-84)	65 (32-85)	65 (20-87)	< .001	NS	< .001	< .001
Time from symptoms to SM diagnosis, mo		33 (0-516)	72 (0-516)	18 (0.7-372)	15.1 (0.6-360)	< .001	NS	< .001	< .001
Clinical characteristics									
Urticaria pigmentosa	140 (41)		100 (63)	15 (37)	25 (18)	.002	.01	< .001	< .001
Cutaneous symptoms*	182 (53)		119 (75)	20 (49)	42 (30)	.001	.03	< .001	< .001
Constitutional symptoms†	142 (42)		30 (19)	24 (59)	85 (62)	< .001	NS	< .001	< .001
Mediator-related symptoms‡	160 (47)		110 (69)	9 (22)	39 (28)	< .001	NS	< .001	< .001
Idiopathic and/or recurrent anaphylactoid reaction	57 (17)		53 (33)	2 (5)	2 (1)	< .001	NS	< .001	< .001
Musculoskeletal symptoms§	107 (31)		48 (30)	17 (41)	41 (30)	NS	NS	NS	.3
Gastrointestinal symptoms‖	221 (65)		113 (71)	26 (63)	79 (57)	NS	NS	.01	.05
Hepatomegaly	92 (27)		22 (14)	16 (39)	53 (38)	< .001	NS	< .001	< .001
Splenomegaly, N = 335	123 (37)		26 (17)	18 (44)	76 (57)	< .001	NS	< .001	< .001
Both hepatomegaly and splenomegaly, N = 335	72 (21)		15 (10)	13 (32)	43 (32)	< .001	NS	< .001	< .001
Lymphadenopathy¶	73 (21)		22 (14)	11 (27)	40 (29)	.05	NS	.001	.005
B-findings	168 (49)		53 (33)	22 (54)	90 (65)	.02	NS	< .001	< .001
BM MC > 30% or serum tryptase > 200 ng/mL	60 (18)		23 (14)	9 (22)	26 (19)	NS	NS	NS	.4
Hypercellular BM or dysmyelopoiesis, without cytopenias	20 (6)		13 (8)	6 (15)	n/a	NS	n/a	n/a	n/a
Hepatosplenomegaly and/or LNP without functional impairment	144 (42)		41 (26)	18 (44)	83 (60)	.02	NS	< .001	< .001
C-findings	80 (23)		n/a	41 (100)	36 (26)	n/a	< .001	n/a	n/a
BM dysfunction with cytopenia(s)#	17 (5)		n/a	13 (32)	n/a	n/a	n/a	n/a	n/a
Hepatomegaly with functional impairment	31 (9)		n/a	11 (27)	20 (14)	n/a	NS	n/a	n/a
Splenomegaly with hypersplenism	27 (8)		n/a	9 (22)	16 (12)	n/a	NS	n/a	n/a
Osteolysis/pathological fractures	23 (7)		n/a	18 (44)	5 (4)	n/a	< .001	n/a	n/a
Malabsorption with weight loss	3 (1)		n/a	2 (5)	1 (1)	n/a	NS	n/a	n/a
Leukemic transformation, AML or MCL	21 (6)		1 (< 1)	2 (5)	18 (13)	NS	NS	< .001	< .001
Laboratory characteristics									
Hemoglobin, g/L	341 (99)	128 (51-174)	139 (81-167)	113 (51-165)	109 (64-174)	< .001	NS	< .001	< .001
Hb < normal	155 (45)	105 (51-134)	28 (18)	24 (59)	99 (72)	< .001	NS	< .001	< .001
Hb < 100	64 (19)	90 (51-99)	4 (3)	10 (24)	48 (35)	< .001	NS	< .001	< .001

ISM indicates indolent systemic mastocytosis (SM); ASM, aggressive SM; SM-AHNMD, SM with associated clonal hematologic non–mast cell lineage disease; MCL, mast cell leukemia; AML, acute myeloid leukemia; No., number; BM, bone marrow; ANC, absolute neutrophil count; AMC, absolute monocyte count; ALC, absolute lymphocyte count; AEC, absolute eosinophil count; LNP, lymphadenopathy; SAP, serum alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; PG prostaglandin; g, grams; dL, deciliter; L, liter; UNL upper normal limit; WNL, within normal limits; U, units; μg, micrograms; mg, milligrams; ng, nanograms; Cr, creatinine; NS, not significant; and n/a, not applicable.

*, †, ‡, §, ‖, and ¶, please see Table 1 legend.

#Absolute neutrophil count < 1.0 $\times 10^9$/L; hemoglobin < 100 g/L; or platelet count < 100 $\times 10^9$/L.

Table 3. Comparison of demographic, clinical, and laboratory characteristics between SM subgroups (continued)

Characteristic	No. (%) of patients	Median (range)	ISM	ASM	SM-AHNMD	*P* for ISM vs ASM	*P* for ASM vs AHNMD	*P* for ISM vs AHNMD	Overall *P*
White blood cell count, $\times 10^9$/L	340 (99)	7.6 (1.2-87.2)	6.6 (1.6-19.3)	8.2 (1.7-37.1)	10.2 (1.2-87.2)	.01	NS	< .001	< .001
WBC > 10	109 (32)	15.4 (10.1-87.2)	22 (14)	17 (41)	70 (51)	< .001	NS	< .001	< .001
WBC 4-10	198 (58)	6.6 (4.1-10)	124 (79)	21 (51)	50 (36)	< .001	NS	< .001	< .001
ANC, $\times 10^9$/L	333 (97)	4.3 (0.2-42.5)	4.2 (0.6-12.4)	4.2 (0.9-17.8)	4.8 (0.2-42.5)	NS	NS	NS	.3
ANC < 1.0	15 (5)	0.7 (0.2-1)	2 (1)	2 (5)	11 (8)	NS	NS	.005	.02
AMC, $\times 10^9$/L	333 (97)	0.4 (0-81)	0.3 (0-81)	0.5 (0-5.2)	0.7 (0-11.2)	.003	NS	< .001	< .001
ALC, $\times 10^9$/L	333 (97)	1.9 (0-15.8)	1.9 (0.1-7.6)	1.9 (0.5-7.4)	1.7 (0.3-15.8)	NS	NS	NS	.5
AEC, $\times 10^9$/L	332 (97)	0.2 (0-38.4)	0.1 (0-2.1)	0.2 (0-9.2)	0.4 (0-38.4)	.02	NS	< .001	< .001
AEC 1.5 or more	49 (15)	3.8 (1.5-38.4)	2 (1)	10 (25)	37 (28)	< .001	NS	< .001	< .001
Platelet count, $\times 10^9$/L	334 (98)	212 (2-1625)	260 (39-570)	179 (20-561)	129 (2-1625)	.001	NS	< .001	< .001
PLT < 150	101 (30)	79 (2-149)	6 (4)	16 (39)	76 (55)	< .001	NS	< .001	< .001
PLT < 100	65 (19)	58 (2-97)	2 (1)	11 (27)	50 (37)	< .001	NS	< .001	< .001
Albumin, 35-50 g/L	265 (77)	39 (20-51)	41 (30-51)	38 (20-48)	38 (20-49)	< .001	NS	< .001	< .001
Albumin < 35	51 (19)	31 (20-34)	10 (9)	10 (26)	29 (27)	.005	NS	.001	.001
Total protein, 63-79 g/L	265 (77)	72 (47-94)	73 (60-89)	73 (55-85)	70 (47-94)	NS	NS	.007	.03
WNL	210 (79)	72 (63-79)	101 (87)	28 (76)	78 (72)	NS	NS	.006	.02
SAP, 45-115 U/L	318 (93)	181 (19-3680)	142.5 (43-1957)	269.5 (33-3375)	206.5 (19-3680)	< .001	NS	< .001	< .001
SAP > UNL	127 (40)	395 (111-3680)	36 (25)	24 (60)	65 (50)	< .001	NS	< .001	< .001
AST, 8-48 U/L	320 (94)	18 (1-194)	19 (1-194)	17 (6-93)	18 (5-185)	NS	NS	NS	1
AST > UNL	37 (12)	46 (32-194)	10 (7)	5 (13)	22 (17)	NS	NS	.008	.03
ALT, 7-55 U/L	99 (29)	20 (4-222)	19.5 (6-117)	15 (4-122)	21.5 (7-222)	NS	NS	NS	.3
ALT > UNL	10 (10)	82 (47-222)	4 (7)	1 (9)	5 (16)	NS	NS	NS	.4
Total bilirubin, 1.7-17.1 μM/L	292 (85)	12 (1.7-133.4)	10.3 (1.7-68.4)	12 (3.4-88.9)	13.7 (3.4-133.4)	NS	NS	< .001	< .001
T bili > UNL	65 (22)	25.7 (18.8-133.4)	13 (11)	10 (28)	42 (32)	.01	NS	< .001	< .001
LDH, 122-222 U/L	164 (48)	150.5 (11-926)	127 (11-283)	146 (97-390)	170.5 (46-926)	NS	NS	< .001	< .001
LDH > UNL	28 (17)	324.5 (213-926)	2 (4)	1 (9)	25 (25)	NS	NS	.001	.002
Ferritin, 20-300 μg/L	105 (31)	215.9 (6-17 980)	81 (7-384)	332.5 (37-2244)	328 (6-17 980)	.002	NS	< .001	< .001
> UNL	47 (45)	658 (207-17 980)	5 (18)	7 (58)	34 (54)	.02	NS	.001	.004
Serum tryptase, < 11.5 ng/mL	160 (47)	63.6 (3.7-2000)	53.6 (11.4-1410)	145 (10-2000)	75.4 (3.7-1360)	.02	NS	NS	.03
Tryptase 11.5 or less	154 (96)	66.6 (11.9-2000)	89 (99)	14 (93)	49 (92)	NS	NS	NS	.08
Tryptase 200 or more	33 (21)	303 (200-2000)	11 (12)	6 (40)	15 (28)	.007	NS	.02	.009
Urine histamine, < 35 μg/g Cr/24 h	58 (17)	62.3 (12-985.6)	49 (17-985.6)	210.1 (105-409)	85.6 (12-843)	.01	NS	NS	.05
U histamine 35 or more	41 (71)	107.6 (36.7-985.6)	21 (62)	4 (100)	15 (79)	NS	NS	NS	.2
Urine *N*-methylhistamine, 30-200 μg/g Cr	64 (19)	354.5 (5-5447)	335 (33-4156)	445 (37-775)	1332.5 (5-5447)	NS	NS	NS	.4
U M-histamine > UNL	52 (81)	508.5 (98-5447)	41 (80)	6 (86)	5 (83)	NS	NS	NS	.9
Urine beta PGF2α, 1000 ng or less/24 h	99 (29)	2215 (119-21 608)	1880 (119-13 100)	1952 (184-21 608)	4083 (572-18 680)	NS	NS	.007	.03
U PGF2α > UNL	74 (75)	3262 (1132-21 608)	50 (69)	9 (82)	14 (93)	NS	NS	NS	.1

ISM indicates indolent systemic mastocytosis (SM); ASM, aggressive SM; SM-AHNMD, SM with associated clonal hematologic non–mast cell lineage disease; MCL, mast cell leukemia; AML, acute myeloid leukemia; No., number; BM, bone marrow; ANC, absolute neutrophil count; AMC, absolute monocyte count; ALC, absolute lymphocyte count; AEC, absolute eosinophil count; LNP, lymphadenopathy; SAP, serum alkaline phosphatase; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; PG prostaglandin; g, grams; dL, deciliter; L, liter; UNL upper normal limit; WNL, within normal limits; U, units; μg, micrograms; mg, milligrams; ng, nanograms; Cr, creatinine; NS, not significant; and n/a, not applicable.

*, †, ‡, §, ‖, and ¶, please see Table 1 legend.

#Absolute neutrophil count < 1.0 $\times 10^9$/L; hemoglobin < 100 g/L; or platelet count < 100 $\times 10^9$/L.

Table 4. Bone marrow histopathologic findings at referral of 342 patients with SM

Bone marrow characteristics	No (%) of patients	Median (range)	ISM	ASM	SM-AHNMD	*P*
BM cellularity corrected for age, N = 327		70 (20-100)	50 (20-100)	75 (30-100)	90 (30-100)	< .001
High	200 (61)		49 (32)	24 (67)	123 (91)	
Normal	108 (33)		88 (58)	9 (25)	11 (8)	
Low	19 (6)		15 (10)	3 (8)	1 (1)	
BM % MC, N = 299		10 (1-90)	10 (1-90)	13 (1-70)	11 (1-70)	.2
BM MC < 10	109 (36)		58 (41)	9 (26)	42 (35)	.1
BM MC 10-30	151 (51)		68 (48)	17 (50)	66 (55)	
BM MC > 30	39 (13)		15 (11)	8 (24)	12 (10)	
BM MC nuclear morphology, N = 259						.002
Oval	191 (74)		87 (78)	21 (66)	82 (73)	
Elongated	48 (19)		24 (22)	7 (22)	17 (15)	
Indented/lobulated	16 (6)		0	3 (9)	10 (9)	
Round	4 (2)		0	1 (3)	3 (3)	
BM MC granularity, N = 243						
Normal to > 50%	164 (67)		86 (82)	16 (50)	61 (60)	< .001
BM % blast, N = 342						< .001
BM blast < 5	315 (92)		159 (100)	41 (100)	111 (80)	
BM blast 5-10	16 (5)		0	0	16 (12)	
BM blast > 10	11 (3)		0	0	11 (8)	
BM eosinophil infiltration grade, N = 257						< .001
Absent	27 (11)		8 (7)	5 (16)	11 (10)	
Minimal to moderate	207 (81)		99 (91)	25 (78)	82 (73)	
Intense	23 (9)		2 (2)	2 (6)	19 (17)	
BM fibrosis grade, N = 122						
2+ or more	44 (36)		5 (14)	8 (47)	31 (46)	.004
BM MC immunophenotype (flow cytometry), N = 70						
CD2 positivity	38 (54)		27 (66)	4 (50)	7 (33)	.05
CD25 positivity	65 (93)		39 (95)	8 (100)	18 (86)	.4
BM MC immunophenotype (immunohistochemistry)						
CD2 positivity, N = 18	3 (17)		2 (15)	n/a	1 (20)	n/a
CD25 positivity, N = 23	23 (100)		15 (100)	n/a	8 (100)	n/a

ISM indicates indolent systemic mastocytosis (SM); ASM, aggressive SM; SM-AHNMD, SM with associated clonal hematologic non–mast cell lineage disease; %, percentage; BM, bone marrow; MC, mast cell; No., number; and n/a, not accessed or not applicable.

Cytogenetic and molecular studies

Cytogenetic data were available for 186 (54%) patients, 37 of whom (20%) had chromosomal aberrations (excluding 5 patients with sole deletion of chromosome Y). Recurrent chromosomal abnormalities included trisomy 8, monosomy 7, del(13q), del(5q), trisomy 10, del(20q), trisomy 6, trisomy 19, and trisomy X. Abnormal karyotype was more frequently detected in SM-AHNMD (31%) and ASM (20%), as opposed to ISM (5%; $P < .001$). All 7 patients with more than one chromosomal abnormality had SM-AHNMD. Fifty-six patients displayed prominent eosinophilia; 52% of 23 patients screened for *FIP1L1-PDGFRA* and 62% of 34 patients screened for *KIT*D816V carried the mutation. Eight patients with eosinophilia were screened for *FIP1L1-PDGFRA* and *KIT*D816V: there were no instances of concomitant presence of these mutations. Archived bone marrow was available in 165 (48%) patients for *KIT*D816V and *JAK2*V617F analysis. By allele-specific PCR, *KIT*D816V mutation was detected in 113 patients (68%): ISM, 78%; ASM, 82%; and SM-AHNMD, 60% ($P = .03$). The sole MCL leukemia patient who was tested did not harbor this mutation. *JAK2*V617F mutation was detected (mutant allele burden > 1%) in 6 patients (4%); all had SM-AHNMD, including 4 with non-MC lineage myeloproliferative neoplasm. Five (83%) of the 6 patients harbored *KIT*D816V and *JAK2*V617F mutations concomitantly.

Survival studies and leukemic transformation

After a median follow-up of 20.7 months (range = 0-417 months), 153 (45%) deaths were recorded (26 ISM, 25 ASM, 99 SM-AHNMD, 3 MCL). The median survival of the cohort was 63 months, which is inferior compared with the age- and sex-matched US population (Figure 1A). Survival in patients with ISM (median, 198 months) was superior ($P < .001$) to that of patients with ASM (median, 41 months), SM-AHNMD (median, 24 months), or MCL (median, 2 months) and not significantly different from that of the control population (Figure 1B). Information regarding the cause of death was available for 13 (50%) of the 26 ISM patients: disease progression to ASM (n = 3), development of solid tumors (n = 3), comorbid cardiovascular conditions (n = 3), complications from massive MC mediator release (n = 2), acute myeloid leukemia (n = 1), and infection (n = 1). Among 21 (6%) cases of leukemic transformation in the overall cohort (18 with AML and 3 MCL), 18 (86%) occurred in the setting of SM-AHNMD; 2, ASM; and 1, ISM ($P < .001$; Table 3).

Prognostic factors

In addition to specific diagnosis based on the WHO proposal, other demographic, clinical, and laboratory variables were examined for their prognostic relevance (Table 5). In this regard, the pitfalls of considering multiple variables must be kept in mind and certain variables (eg, splenomegaly, hypoalbuminemia; identified by § in Table 5) represent B- or C-findings and are therefore already accounted for in the WHO classification. Multivariable analysis showed a significant and independent association between inferior survival and WHO subtype ($P < .001$), advanced age ($P < .001$), history of weight loss ($P = .01$), anemia ($P = .007$), thrombocytopenia ($P < .001$), hypoalbuminemia ($P < .001$), and excess BM blasts (> 5%; $P = .004$).

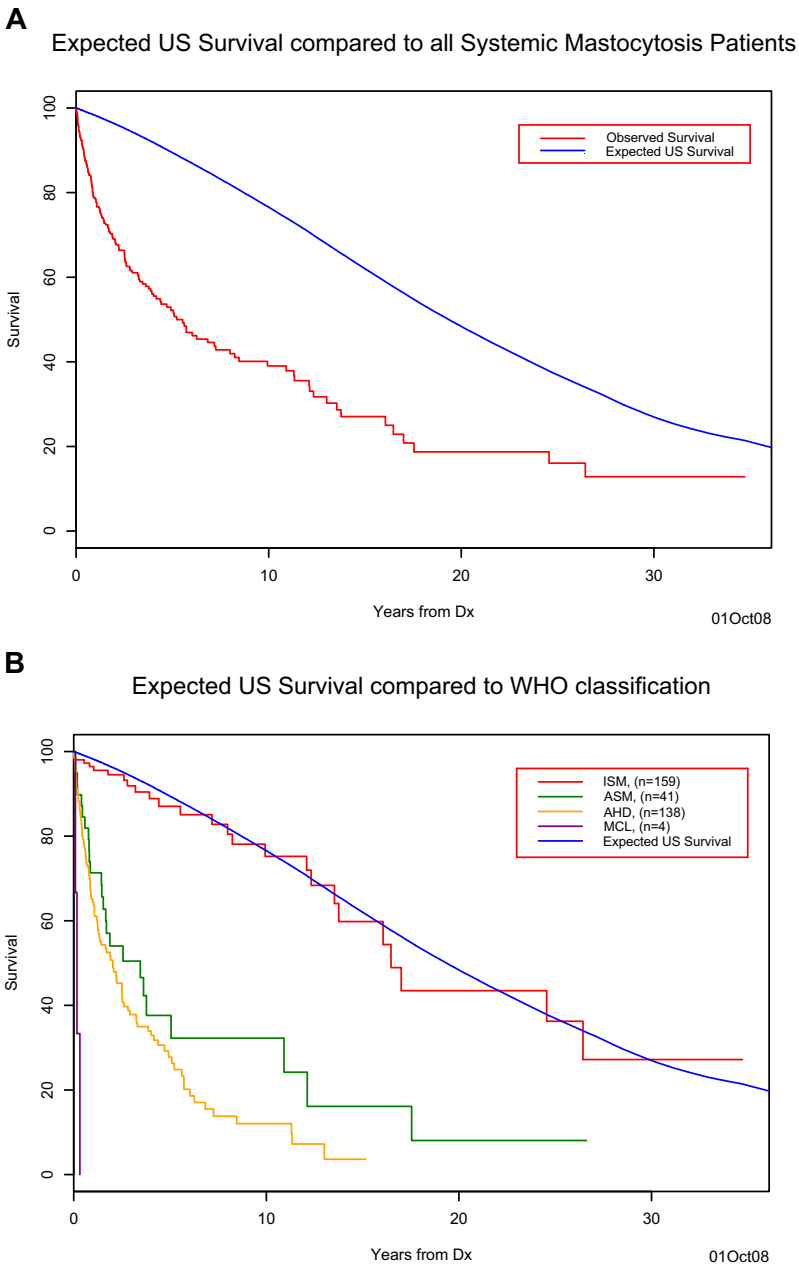

Figure 1. Survival of systemic mastocytosis patients. (A) The observed Kaplan-Meier survival for systemic mastocytosis patients (red) compared with the expected age- and sex-matched US population's survival (blue). (B) The observed Kaplan-Meier survival for systemic mastocytosis patients classified by disease type ISM (red), ASM (green), AHNMD (yellow), and MCL (purple) compared with the expected age- and sex-matched US population's survival (blue) for the entire cohort.

Discussion

To our knowledge, the current study is the largest SM series reported in the literature. The clinical findings pertain to an adult SM population with bone marrow histology–confirmed disease that was seen at a tertiary care center. Consequently, extrapolation to an SM population identified primarily on the basis of UP-like skin lesions, or one that includes pediatric patients, may not be valid.

Consistent with previous studies, the current cohort had a slight male preponderance; the relatively long duration between onset of symptoms and diagnosis is consistent with absence of UP-like skin lesions in a majority of patients, and also to the referral nature of our practice. The life expectancy of SM patients was shorter relative to age- and sex-matched controls. As initially observed by Travis et al,[2] survival decreased rapidly after diagnosis: to 60% at 3 years, with a subsequent slower decline to 50% at 5 years. Beyond 5 years, the slope of the survival curve was similar to that of the control population. This observation confirms that the excess deaths in SM patients occur within the first 3 (and up to 5) years after diagnosis.

The current study validates the prognostic relevance of the WHO classification for SM. Patients with ISM have a significantly better prognosis in terms of overall survival and leukemia-free survival compared with ASM and SM-AHNMD patients. Furthermore, the life expectancy of ISM patients was not significantly different from the age- and sex-matched US population for the appropriate time period based on the diagnosis date. Furthermore, leukemic transformation rarely occurs in ISM patients. In contrast, the median survival of SM-AHNMD and ASM patients was 2 and 3.5 years, respectively; MCL patients, not surprisingly, had the poorest prognosis with median survival of 2 months. These data are clinically relevant and serve as a basis for guiding therapeutic decisions in SM patients. It supports the view that, in general, therapy for ISM ought to be symptom directed and potentially immunosuppressive and leukemogenic therapies are best avoided

Table 5. Unfavorable prognostic factors in SM by univariate analysis

Prognostic factor	No. of patients	No. of deaths	Median survival, mo	*P*, log-rank test
Age, y				
Younger than 65	222	64	163	< .001
65 or older	120	89	24	
Sex				
Female	154	60	136	.001
Male	188	93	45	
WHO variant				
ISM	159	26	198	< .001
ASM	41	25	41	
SM-AHNMD	138	99	24	
MCL	4	3	2	
Symptoms and signs				
Urticaria pigmentosa				
No	202	113	34	< .001
Yes	140	40	163	
Cutaneous symptoms*				
No	160	95	34	< .001
Yes	182	58	146	
Constitutional symptoms†				
No	200	57	145	< .001
Yes	142	96	20	
Mediator-related symptoms‡				
No	182	103	41	< .001
Yes	160	50	146	
Weight loss				
No	224	67	136	< .001
Yes	118	86	17	
Splenomegaly§				
No	212	60	156	< .001
Yes	123	88	25	
Hepatomegaly§				
No	250	87	96	< .001
Yes	92	66	30	
Lymphadenopathy§				
No	269	109	82	.005
Yes	73	44	38	
Laboratory findings				
Anemia				
No	186	45	165	< .001
Yes	155	108	20	
Thrombocytopenia				
No	233	70	136	< .001
Yes	101	78	15	
Leukocytosis				
No	231	82	136	< .001
Yes	109	71	25	
Absolute eosinophil count 1.5×10^9/L or more				
No	283	115	75	< .001
Yes	49	34	18	
PB immature myeloid cells				
No	244	79	136	< .001
Yes	89	71	13	
Ferritin level > 300 μg/L				
No	58	25	66	< .001
Yes	47	36	17	
SAP > UNL				
No	191	66	119	< .001
Yes	127	81	24	

No. indicates number; ISM indicates indolent systemic mastocytosis (SM); ASM, aggressive SM; SM-AHNMD, SM with associated clonal hematologic non–mast cell lineage disease; MCL, mast cell leukemia; dL, deciliter; L, liter; UNL upper normal limit; μg, micrograms; mg, milligrams; ng, nanograms; AST, aspartate transaminase; SAP, serum alkaline phosphatase; LDH, lactate dehydrogenase; BM, bone marrow; MC, mast cell; and NR, not reached.

*Includes pruritus, flushing, urticaria, and angioedema.

†Includes weight loss, fever, chills, and night sweats.

‡Includes headache, dizziness/lightheadedness, syncope/presyncope, hypotension, anaphylaxis, palpitation/tachycardia, bronchoconstriction/wheezing, and peptic ulcer disease.

§Represent B- or C-findings per the 2001 WHO classification of SM.

Table 5. Unfavorable prognostic factors in SM by univariate analysis (continued)

Prognostic factor	No. of patients	No. of deaths	Median survival, mo	*P*, log-rank test
AST > UNL				
No	283	123	69	.004
Yes	37	22	24	
Hypoalbuminemia§				
No	215	98	82	< .001
Yes	50	34	12	
LDH > UNL				
No	136	60	57	.008
Yes	28	20	20	
Total bilirubin > 18.8 μM/L				
No	237	101	82	< .001
Yes	55	41	15	
Serum tryptase level > 200 ng/mL				
No	127	20	136	< .001
Yes	33	19	30	
Bone marrow findings				
BM cellularity§				
Low	19	1	NR	< .001
Normal	108	13	295	
High§	200	128	30	
BM MC 30% or more§				
No	235	82	96	< .001
Yes	64	45	30	
BM blasts 5% or more				
No	315	131	72	< .001
Yes	27	22	11	
BM fibrosis grade 2+ or more				
No	78	41	61	< .001
Yes	44	32	18	
Karyotype				
Normal	144	68	53	.002
Abnormal	42	33	13	

No. indicates number; ISM indicates indolent systemic mastocytosis (SM); ASM, aggressive SM; SM-AHNMD, SM with associated clonal hematologic non–mast cell lineage disease; MCL, mast cell leukemia; dL, deciliter; L, liter; UNL upper normal limit; μg, micrograms; mg, milligrams; ng, nanograms; AST, aspartate transaminase; SAP, serum alkaline phosphatase; LDH, lactate dehydrogenase; BM, bone marrow; MC, mast cell; and NR, not reached.

*Includes pruritus, flushing, urticaria, and angioedema.

†Includes weight loss, fever, chills, and night sweats.

‡Includes headache, dizziness/lightheadedness, syncope/presyncope, hypotension, anaphylaxis, palpitation/tachycardia, bronchoconstriction/wheezing, and peptic ulcer disease.

§Represent B- or C-findings per the 2001 WHO classification of SM.

in these patients given the relatively good prognosis and normal life expectancy.[19,20] For patients with ASM or MCL, or the rare ISM patient with recurrent severe anaphylaxis or syncope not responding to conventional approaches, the goal of therapy is to reduce the systemic MC burden. Published data suggest that interferon-alpha and 2-chlorodeoxyadenosine (2-CdA) have significant inhibitory activity against the malignant MC clone, however both agents are plagued by problems, namely, poor tolerability and uncertainty regarding optimal dose/duration of therapy (IFN-α), or potential mutagenic effects, myelosuppression, and immunosuppression (2-CdA).[21,22] Imatinib is relatively ineffective in *KIT*D816V-positive SM,[23] however may have activity in the rare SM case with other KIT mutations (eg, *KIT*F522C),[24] or in patients with eosinophilia and MC proliferation who harbor the *FIP1L1-PDGFRA* mutation.[25-27] Preliminary data suggest that dasatinib has limited therapeutic activity in SM[28,29]; however, its role in combination with chemotherapeutic agents is under active investigation.[30,31]

In the WHO proposal, "B-" and "C-"findings serve as surrogate markers for a high MC burden, and impaired organ function resulting therefrom, respectively, and are used to classify SM patients. Given that B- and C-findings have been defined somewhat arbitrarily (for instance, is Hgb < 100 g/L [10 g/dL] as prognostically relevant as Hgb < 80 g/L [8 g/dL], or Hgb < normal? Similarly, is presence of pathologic fracture as prognostically relevant as hypoalbuminemia?), we conducted a multivariate analysis to identify those variables that may have prognostic relevance within the context of the WHO subgroups. Among the demographic variables, advanced age (≥ 65 years) was independently associated with shorter survival. Anemia and thrombocytopenia were also independently associated with shorter survival; notably, the threshold for identifying poor risk patients was lower than the corresponding C-findings (defined as hemoglobin < 100 g/L [10 g/dL] and platelet count < 100×10^9/L). Weight loss and hypoalbuminemia were also independently associated with shorter survival regardless of whether this resulted from malabsorption. Among the histologic variables, only excess BM blasts (> 5%) was independently associated with shorter survival. It has been reported that the percentage of MCs in BM smears may distinguish between clinical variants of SM[32]; this aspect was not examined in our study because MCs were quantified only in trephine biopsy specimens.

In the current analysis, prevalence of *KIT*D816V using a sensitive (0.01%) assay was broadly consistent with published data,[11] considering our use of DNA from unfractionated BM cells. Detection of *KIT*D816V was not significant in the survival analysis; however, the mutation was significantly associated with presence of C-findings (83% vs 64%; $P = .03$) and higher BM MC

burden (median, 13% vs 10%; $P = .01$). *JAK2*V617F was infrequently detected in SM patients and appeared to be restricted to SM-AHNMD, where it frequently coexisted with *KIT*D816V. In contrast, none of the *FIP1L1-PDGFRA*–positive patients in our cohort harbored *KIT*D816V, an observation that is consistent with the complete clinical and histologic responses seen with imatinib therapy in these patients.

In summary, we have described the clinical, laboratory, and BM histologic features at presentation in a large cohort of adult SM patients. Survival of this cohort is shorter relative to an age- and sex-matched control population. When patients are classified into WHO subgroups, there are significant differences in disease characteristics. ISM patients have a normal life expectancy and leukemic transformation is rarely seen in these patients; in contrast, the other SM subgroups have a significantly poorer prognosis. We have validated the prognostic relevance of the WHO proposal for SM, and have identified additional risk factors (advanced age, weight loss, anemia, thrombocytopenia, hypoalbuminemia, and excess bone marrow blasts) that are significantly associated with shorter survival.

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Authorship

Contribution: K.-H.L. collected and analyzed the data and wrote the paper; A.T. designed the study, analyzed the data, and wrote the paper; T.L.L. and C.F. performed the molecular analysis; M.P. and J.H.B. collected and analyzed the data; R.F.M. performed the KIT mutation analysis; C.-Y.L. performed the bone marrow histology analysis; and A.P. designed the study, analyzed the data, and wrote the paper.

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