CME Information: Systemic mastocytosis in adults: 2017 update on diagnosis, risk stratification and management

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- Identify the current pathogenetic concepts, classification, diagnosis, and risk stratification of systemic mastocytosis
- Identify the current management of systemic mastocytosis, including updates in investigational therapies

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ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES
AJH Educational Material

Systemic mastocytosis in adults: 2017 update on diagnosis, risk stratification and management

Animesh Pardanani*

Disease overview: Systemic mastocytosis (SM) results from a clonal proliferation of abnormal mast cells (MC) in one or more extra-cutaneous organs.

Diagnosis: The major criterion is presence of multifocal clusters of morphologically abnormal MC in the bone marrow. Minor diagnostic criteria include elevated serum tryptase level, abnormal MC expression of CD25 and/or CD2, and presence of *KIT*D816V.

Risk stratification: The 2008 World Health Organization (WHO) classification of SM has been shown to be prognostically relevant. Classification of SM patients into indolent (SM), aggressive SM (ASM), SM associated with a clonal non-MC lineage disease (SM-AHNMD) and mast cell leukemia (MCL) subgroups is a useful first step in establishing prognosis.

Management: SM treatment is generally palliative. ISM patients have a normal life expectancy and receive symptom-directed therapy; infrequently, cytoreductive therapy may be indicated for refractory symptoms. ASM patients have disease-related organ dysfunction; interferon-α (±corticosteroids) can control dermatological, hematological, gastrointestinal, skeletal and mediator-release symptoms, but is hampered by poor tolerability. Similarly, cladribine has broad therapeutic activity, with particular utility when rapid MC debulking is indicated; the main toxicity is myelosuppression. Imatinib has a therapeutic role in the presence of an imatinib-sensitive KIT mutation or in *KIT*D816-unmutated patients. Treatment of SM-AHNMD is governed primarily by the non-MC neoplasm; hydroxyurea has modest utility in this setting; there is a role for allogeneic stem cell transplantation in select cases.

Investigational drugs: Recent data confirms midostaurin's significant anti-MC activity in patients with advanced SM.

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Disease Overview and Pathogenesis

Mastocytosis is one of eight subcategories of myeloproliferative neoplasms (MPN) per the 2008 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues [1]. It results from a clonal, neoplastic proliferation of morphologically and immunophenotypically abnormal mast cells (MC) that accumulate in one or more organ systems. The sine qua non of mastocytosis is the presence of multifocal clusters of abnormal MC, which in contrast to normal MC are variable in appearance, ranging from round to fusiform variants with long, polar cytoplasmic processes, and may display cytoplasmic hypogranularity with uneven distribution of fine granules, as well as atypical nuclei with monocytoid appearance [2–4].

The clinical presentation of mastocytosis is heterogeneous, ranging from skin-limited disease (cutaneous mastocytosis, CM), particularly in pediatric cases where the majority have disease-onset within the first 2 years of life and commonly experience spontaneous regression of skin lesions [5–8], to a more aggressive variant with extracutaneous involvement (systemic mastocytosis, SM) that may be associated with multiorgan dysfunction/failure and shortened survival, that is generally seen in adult patients (Fig. 1) [9].

The WHO document distinguishes the usually *KIT*-mutated SM from a Philadelphia chromosome-negative MPN with hematological features of chronic eosinophilic leukemia associated with splenomegaly, marked elevation of serum vitamin B_{12}, elevation of serum tryptase and increased bone marrow (BM) MC commonly in scattered or non-cohesive clusters [10]. The latter entity is commonly associated with rearrangement of *PDGFRA* (i.e., *FIP1L1-PDGFR*) and less commonly, *PDGFRB* (e.g., *PRKG2-PDGFRB)*, and is sensitive to treatment with imatinib [11–18]. WHO-defined SM is sometimes associated with a clonally-related second myeloid neoplasm [19–22], which is not surprising considering its origin as a stem cell disease with multilineage clonal involvement [23–25]. Conversely, an otherwise well-defined myeloid malignancy, such as myelodysplastic syndrome (MDS) or a nonmast cell disease MPN, might also harbor neoplastic mast cells [26].

Mastocytosis is frequently associated with somatic gain-of-function point mutations within *KIT*. KIT (CD117) is a Type III receptor tyrosine kinase that is expressed by MC, hematopoietic progenitor cells, germ cells, melanocytes and interstitial cells of Cajal in the gastrointestinal tract and is therefore functionally relevant for normal mast cell development, hematopoiesis, gametogenesis, melanogenesis, and regulation of slow gastric waves [27]. KIT expression is down regulated upon differentiation of hematopoietic progenitors into mature cells of all lineages, except mast

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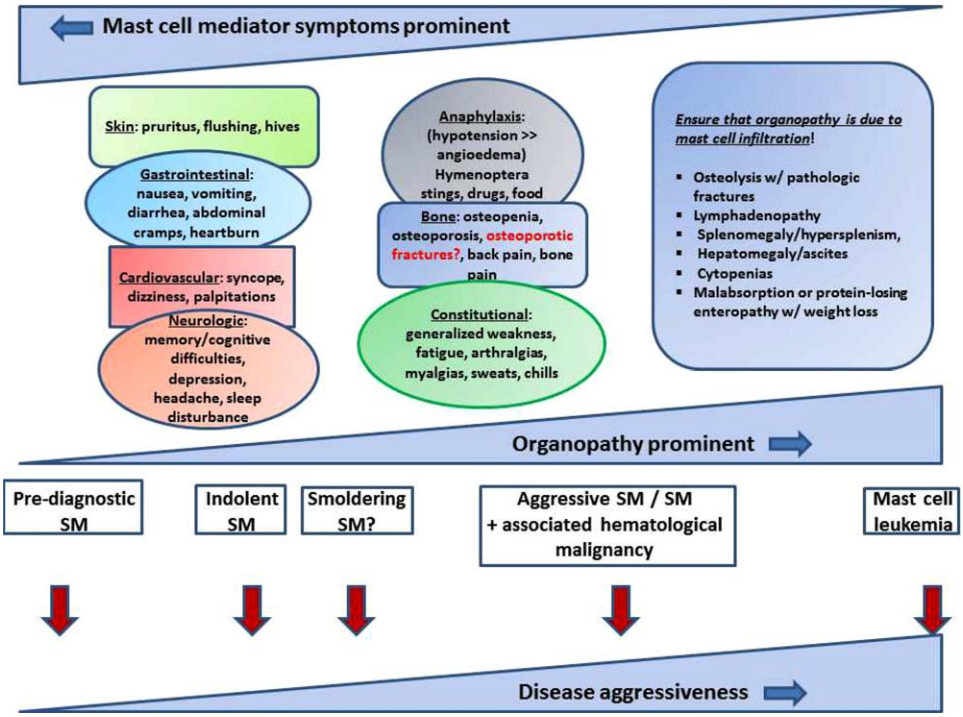

Figure 1. Clinical spectrum of patients with clonal mast cell disorders. Please refer to Tables I and II for the World Health Organization classification of mastocytosis. "Pre-diagnostic' systemic mastocytosis (SM) refers to an abnormal clonal bone marrow mast cell infiltrate that falls short of the diagnostic threshold for SM (generally satisfies 1–2 minor criteria only).

cells, which retain high levels of cell surface KIT expression. The interaction between KIT and its ligand, stem cell factor (SCF), plays a key role in regulating mast cell proliferation, maturation, adhesion, chemotaxis, and survival [28].

Gain-of-function somatic mutations in the *KIT* tyrosine kinase domain, particularly the D816V mutation, have been found to occur in a majority of cases of adult SM, irrespective of WHO SM subtype [9,29]. Other less common (<5%) somatic *KIT* mutations identified in adult SM include V560G [30,31], D815K [32], D816Y [29,32–34], insVI815-816 [29], D816F [32,34], D816H [35], and D820G [36]. Recent studies have confirmed that childhood-onset mastocytosis is also clearly clonal in nature, and is associated with germline or acquired activating *KIT* mutations [37–39]. In one study of pediatric CM that screened the entire *KIT* coding sequence for mutations using skin lesional DNA, only 42% of cases harbored missense mutations targeting *KIT*D816; in 44% of cases, genetic alterations (insertions (insFF419), deletions (Δ419), deletion-insertions (Δ417-419insY), internal tandem duplications (ITD SA501-502, ITD AY502-503, ITD NFAF505-508) and missense mutations (D816V, D816Y, D816I, C443Y, S476I, K509I, D572A, M541L)) were found to mainly involve exons 8 and 9, which encode the fifth Ig (D5) domain and the extracellular region near the transmembrane domain. The aforementioned mutations in the exons 8 and 9 have have been reported in CBF-AML (Δ417-419insY) [40,41], kindreds with familial GISTs and mastocytosis (Δ 419) [42], familial mastocytosis (K509I) [43] and GISTs (ITD AY502-503) [44]. As with *KIT*D816V, every one of the mutations in exons 8 and 9 that was tested was found to constitutively activate KIT kinase activity. Other rare germline *KIT* mutations that target the transmembrane domain and that are associated with familial mastocytosis include F522C and A533D [45,46].

While activating *KIT* mutations are frequently associated with human mastocytosis, they do not occur universally, and the question as to whether individual mutations are necessary and sufficient to cause mast cell transformation and whether such mutations alone explain the diverse clinical presentations of mastocytosis remains currently unsettled. Furthermore, while childhood- and adult-onset mastocytosis are both associated with activating *KIT* mutations, the natural history of the two conditions is quite different, with the former often exhibiting skin-limited disease that spontaneously regresses with age; in contrast, the latter is characterized by persistent multiorgan involvement, often with a concurrent non-MC hematologic neoplasm.

Experimental data with regard to this issue have not been conclusive; in transgenic mice expressing human *KIT*D816V in mature MC (under the control of the chymase promoter), only a subset (30%) of mice developed a limited form of mastocytosis (some with cutaneous-limited disease) at an old age (12–18 months) [47]. Although BM-derived MC from the transgenic animals eventually became growth factor independent and could be maintained in long-term cultures, the incomplete disease penetrance in this model suggested that additional somatic mutations are necessary for full MC transformation. In another transgenic mouse model that allowed conditional expression of murine *KIT*D814V (the homolog of human *KIT*D816V) driven by the *KIT* promoter, expression of mutant KIT in adult mice including in hematopoietic precursors caused severe mastocytosis with 100% penetrance at a young age [48]. Approximately half of the mice developed a non-MC lineage hematologic neoplasm, most frequently a leukemic disease derived from an immature B-cell precursor. The mice also developed a severe focal inflammatory colitis associated with a massive increase in mucosal mast cell numbers. In contrast, when mutant KIT expression in this model was limited to more mature MC, disease expression was significantly attenuated; while half of the mice developed MC tumors and erosive skin lesions and all developed severe colitis, the disease occurred significantly later and progressed much slower. While both the aforementioned transgenic murine models are imperfect (abnormal intracellular processing/trafficking of human KITD816V resulting in low oncogenicity in the former, and low transgene expression in the latter), they cumulatively suggest that the effects of constitutive KIT signaling depend on the developmental stage of the cell targeted by the gain-of-function

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TABLE I. World Health Organization (WHO) Classification of Mastocytosis (Adapted from Ref. [53])

1. Cutaneous mastocytosis (CM):
   (a) Urticaria pigmentosa (UP)/Maculopapular cutaneous mastocytosis (MPCM)
   (b) Diffuse cutaneous mastocytosis
   (c) Solitary mastocytoma of skin
2. Indolent systemic mastocytosis (ISM)
   - Meets criteria for systemic mastocytosis (SM).[b] No "C" findings.[b] No evidence of associated clonal hematological non-mast cell lineage disease.
     (a) Smoldering systemic mastocytosis[a]
   - As above (ISM), but with 2 or more "B" findings, and no "C" findings.[b]
     (b) Isolated bone marrow mastocytosis[a]
   - As above (ISM) with bone marrow involvement, but without skin involvement.
3. Systemic mastocytosis with an associated clonal hematological non-mast cell lineage disease (SM-AHNMD)
   - Meets criteria for SM and criteria for AHNMD as a distinct entity per the WHO classification
4. Aggressive systemic mastocytosis (ASM)
   - Meets criteria for SM. One or more "C" findings.[b] No evidence of mast cell leukemia.
     (a) Lymphadenopathic mastocytosis with eosinophilia
5. Mast cell leukemia (MCL)
   - Meets criteria for SM. Bone marrow biopsy shows a diffuse infiltration, usually compact, by atypical, immature mast cells. BM aspirate smears show ≥20% mast cells. In typical MCL, mast cells account for ≥10% of peripheral blood white cells. Rare variant: aleukemic MCL.
6. Mast cell sarcoma (MCS)
   - Unifocal mast cell tumor. No evidence of SM. Destructive growth pattern. High-grade cytology.
7. Extracutaneous mastocytoma
   - Unifocal mast cell tumor. No evidence of SM. No skin lesions. Non-destructive growth pattern. Low-grade cytology.

[a] Provisional categories.
[b] See Table II for diagnostic criteria for systemic mastocytosis and definition of "B" and "C" findings.

TABLE II. World Health Organization (WHO) Diagnostic Criteria for Systemic Mastocytosis (SM) (Adapted from Ref. [53])

The diagnosis of SM can be made when the major criterion and one minor criterion or at least three minor criteria are present

Major Criterion

Multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organs

Minor Criteria

a. In biopsy sections of bone marrow or other extracutaneous organs, >25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology or, of all mast cells in bone marrow aspirate smears, >25% are immature or atypical
b. Detection of an activating point mutation at codon 816 of *KIT* in bone marrow, blood or other extracutaneous organ
c. Mast cells in bone marrow, blood or other extracutaneous organ express CD2 and/or CD25 in addition to normal mast cell markers¶
d. Serum total tryptase persistently exceeds 20 ng/mL (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid)

"B" findings

1. BM biopsy showing >30% infiltration by MC (focal, dense aggregates) and/or serum total tryptase level >200 ng/mL
2. Signs of dysplasia or myeloproliferation, in non-MC lineage(s), but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm (AHNMD), with normal or slightly abnormal blood counts.
3. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging.

"C" findings

1. Bone marrow dysfunction manifested by one or more cytopenia(s) (ANC $<1.0 \times 10^9$/L, Hgb <10 g/dL, or platelets $<100 \times 10^9$/L), but no obvious nonmast cell hematopoietic malignancy.
2. Palpable hepatomegaly with impairment of liver function, ascites and/or portal hypertension.
3. Skeletal involvement with large osteolytic lesions and/or pathological fractures.
4. Palpable splenomegaly with hypersplenism.
5. Malabsorption with weight loss due to gastrointestinal mast cell infiltrates.

ANC indicates absolute neutrophil count; Hgb, hemoglobin; ng, nanograms; mL, milliliter; L, liter; and dL, deciliter.
Mast cell CD25 expression can be detected by flow cytometry or immunohistochemistry; the latter is probably more reliable and practical in most hematopathology laboratories, and may be the preferred methodology.

mutation. As has been noted in mastocytosis patients [29], mutations targeting undifferentiated progenitors result in multi-lineage involvement and expression of a severe systemic disease phenotype; in contrast, mutations that target committed MC progenitors or mature MC result in milder forms of the disease.

Other oncogenic mutations identified in mastocytosis patients include those in *TET2* (*TET* oncogene family member 2) and *N-RAS* [49,50]. These mutations are not specific to mastocytosis and their pathogenetic role and/or prognostic impact is currently uncertain. *TET2* is a putative tumor suppressor gene; its mutational frequency in SM ranges from 20 to 29% [49,51]. *TET2* mutations co-segregate with *KIT*D816V and functional cooperation between the two mutations appears to enhance oncogenicity of clonal MC, however TET2 mutations do not appear to independently impact survival in SM. Interestingly, expression of an activated M-RAS mutant (Q71L) in primary murine BM cells reproducibly generated a lethal mastocytosis and mast cell leukemia (MCL); in contrast, expression of constitutively activated H-RAS (G21V) produced a lethal histiocytic/monocytic leukemia, presumably reflecting significant differences in downstream signaling pathways in these disease models [52].

Diagnosis

The diagnosis and classification of mastocytosis is based on identification of neoplastic MC by morphological, immunophenotypic, and/or genetic (molecular) criteria using well established criteria as outlined by the 2008 WHO document (Tables I and II; Fig. 2) [1]. Biopsy of organs other than BM, such as liver or spleen, is infrequently pursued, either for diagnostic purposes or to demonstrate MC infiltration as the cause of impaired organ dysfunction. The diagnosis of SM in the absence of skin involvement is considerably more challenging, particularly in those patients with an indolent SM (ISM) variant with low mast cell burden, termed isolated bone marrow mastocytosis (BMM) [53,54]; consequently, a high index of suspicion is required in the setting of recurrent unexplained anaphylaxis, flushing, osteoporosis, gastrointestinal ulcerative disease, or chronic abdominal cramping.

Bone marrow histology

In practice, the current diagnostic approach for SM starts with a BM examination since this site is almost universally involved in adult mastocytosis, and histological diagnostic criteria for non-BM, extracutaneous organ involvement in SM have not been firmly established or widely accepted as of yet. Further, BM examination also allows detection of a second hematologic neoplasm, if present [19,21].

In general, the pathognomonic multifocal dense MC aggregates, frequently in perivascular and/or paratrabecular BM locations (major diagnostic criterion), may not be readily recognized by standard dyes such as Giemsa, particularly when MC exhibit significant

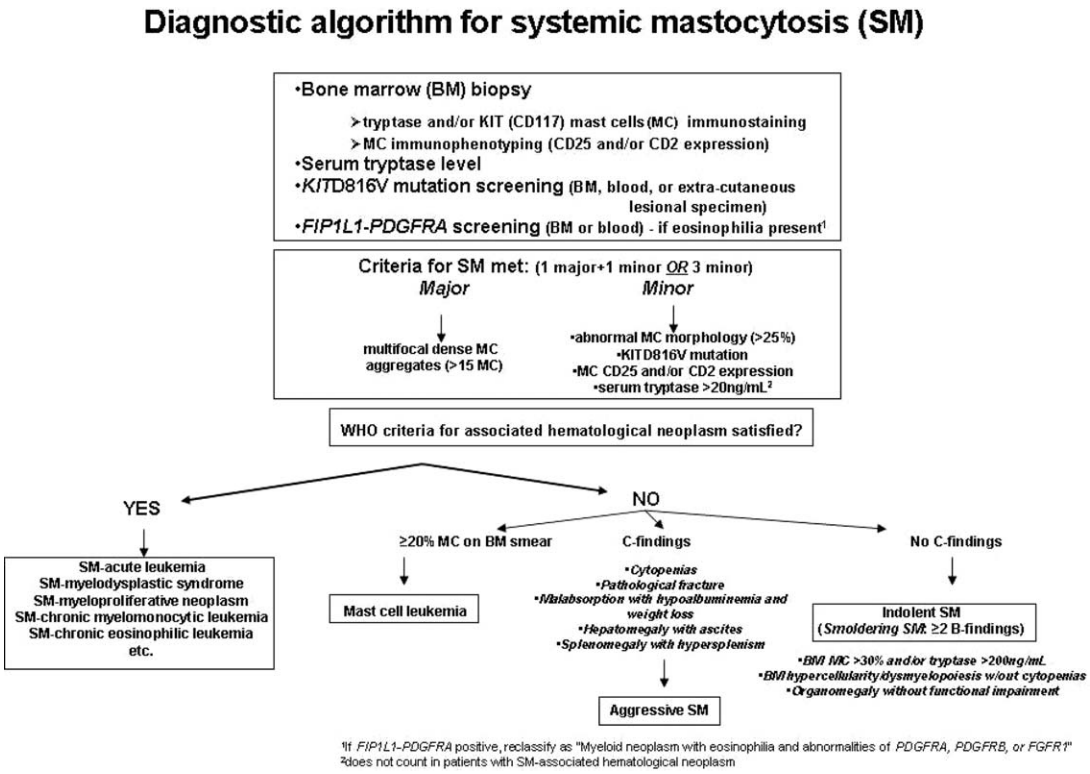

Figure 2. Diagnostic algorithm for systemic mastocytosis.

hypogranulation or abnormal nuclear morphology, or in cases with extensive BM involvement by a second hematological neoplasm (e.g., acute myeloid leukemia), or when significant reticulin fibrosis is present. Among the immunohistochemical markers, tryptase is the most sensitive, given that virtually all MC, irrespective of their stage of maturation, activation status, or tissue of localization express this marker, and consequently allows for detection of even small and/or immature MC infiltrates [55–57]. It must be emphasized however that neither tryptase nor KIT/CD117 immunostaining is able to distinguish between normal and neoplastic MC [58]. Also, abnormal basophils seen in some cases of acute and chronic basophilic leukemia, as well as in chronic myeloid leukemia (CML), and blasts in some AML cases may be tryptase positive, and may prove difficult to distinguish from MC [19].

In contrast, immunohistochemical detection of aberrant CD25 expression on bone marrow MC appears to be a reliable diagnostic tool in SM, given its ability to detect abnormal MC in all SM subtypes, including the rare cases with a loosely scattered, interstitial pattern of MC involvement (see below) [57].

CD30 (Ki-1 antigen) has been reported to be preferentially expressed (proportion of cells as well as intensity of staining) in neoplastic MC from patients with aggressive SM (ASM) or mast cell leukemia (MCL) (11 of 13; 85%) as compared to ISM (12 of 45; 27%) [59]. In the latter group, CD30 expression was significantly correlated with serum tryptase level ≥50 ng/mL. An independent study of 142 SM patients confirmed aberrant CD30 expression (by flow cytometry) on neoplastic MC in a majority of subjects (80%), however, CD30 expression was similar across SM subgroups and there was no clear association between CD30 expression levels and specific clinicopathological characteristics [60]. The clinical implications of this finding are currently unclear given lack of independent confirmation of this relatively subjective assessment, small number of cases studied (particularly ASM/MCL) and overlap of CD30 expression between ISM and ASM/MCL (e.g., SSM cases were uniformly CD30-positive).

Mast cell immunophenotyping

Neoplastic MC generally express CD25 and/or CD2, and the abnormal expression of at least one of these two antigens counts as a minor criterion towards the diagnosis of SM per the WHO system [1]. Expression of CD2 on MC, as assessed by either flow cytometry or immunostaining, has been noted to be variable in SM, and consequently, CD25 expression may be more reliable marker for neoplastic MC [61,62]. The aforementioned immunostaining and immunophenotyping studies enhance the morphological and immunophenotypic distinction between normal (round and CD25-negative) and abnormal (spindle-shaped and CD25-positive) mast cells, respectively [56,62].

Serum tryptase level

Normal MC display a spectrum of 'activation levels' in vivo, and the mechanisms governing the secretory phenotype and mediator release patterns are not completely understood [63]. In SM, an elevated serum tryptase level (>20 ng/mL) counts as a minor diagnostic criterion per the WHO framework [1]; while the levels vary widely, serum tryptase is elevated in the vast majority of SM patients across all WHO subgroups; a significantly greater proportion of ASM and SM-AHNMD patients exhibit a markedly elevated serum tryptase level (>200 ng/mL) compared to those with ISM [9]. Serum tryptase levels are also elevated in a significant proportion of cases with AML, CML and MDS [64]; consequently, this test has limited diagnostic utility in the presence of a second SM-associated myeloid neoplasm. The correlation between MC mediator levels and presence of MC mediator-release symptoms (MCMRS) or systemic MC burden remains incompletely understood; in one study of indolent mastocytosis patients, MC mediator levels were significantly correlated with BM MC burden, but not MCMRS [54].

Molecular studies

Identification of *KIT*D816V counts as a minor diagnostic criterion per the WHO system [1]. Of note, there is a high correlation between

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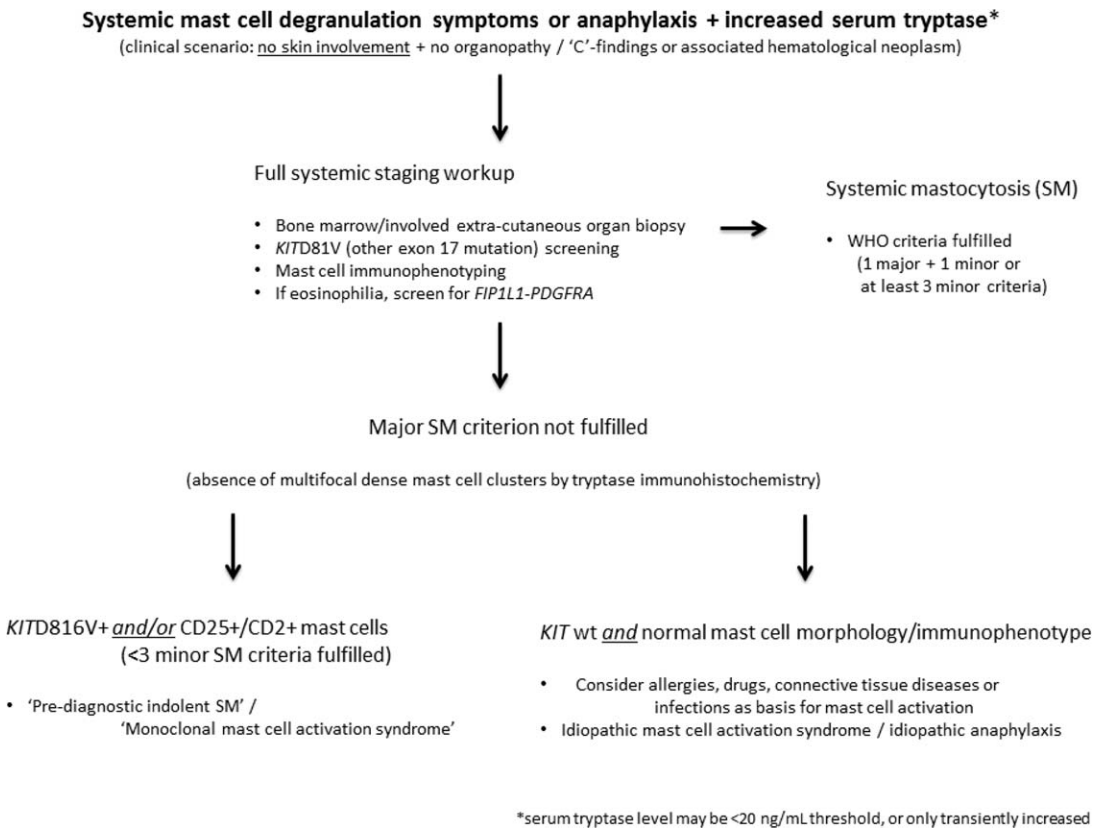

Figure 3. Algorithm for diagnostic assessment of patients presenting with systemic symptoms of mast cell degranulation, without skin involvement by mastocytosis adapted from Ref. [53].

KIT mutation detection and the proportion of lesional cells in the sample, as well as the sensitivity of the screening method employed [65]. Sensitivity of detection may be enhanced by enriching lesional MC by laser capture microdissection, or magnetic bead- or FACS-based cell sorting, respectively [20,29,66], or through the use of highly sensitive PCR techniques [32]. Outside of a research setting, it is currently not standard practice to screen for *KIT* mutations other than those involving D816. The frequency of involvement of non-MC lineages (generally myeloid, but occasionally lymphoid lineages) by *KIT*D816V appears to be greater in cases of ASM or MCL, as compared to ISM [29]. In contrast, *KIT*D816V is variably present in cells representing the second hematological neoplasm in SM with associated clonal hematological non-mast cell lineage disease (SM-AHNMD) cases, depending upon the particular AHNMD subtype (CMML > MPN, AML > lymphoid neoplasms) [67].

Attempts at validating the WHO diagnostic criteria reveal that approximately 20% of ISM patients lack mast cell clusters in the BM and approximately 30% exhibit a serum tryptase level lower than 20 ng/mL [68]. In contrast, the sensitivity for detecting morphologic atypia, aberrant CD25 and/or CD2 expression, or *KIT*D816V in BM mast cells exceeds 90% when sensitive assays are used, thereby illustrating the increasing importance of these specific minor criteria in diagnosing SM [68,69]. Patients who have mast cell degranulation symptoms with clonal mast cells (i.e., mutated *KIT* gene and/or CD25 expression), but who do not meet criteria for SM (only 1 or 2 minor criteria satisfied, and no skin involvement), may have 'pre-diagnostic ISM' or 'monoclonal mast cell activation syndrome' (Fig. 3); these patients generally have normal or slightly elevated baseline serum tryptase level [70]. While the clinical characteristics of this entity may be indistinguishable from ISM, its true natural history remains to be defined.

Rare SM cases may exhibit a well-differentiated phenotype (i.e., relatively normal BM MC morphology; absence of aberrant MC CD25/CD2 expression); these cases are associated with non-D816V *KIT* mutations (e.g., germline F522C or somatic I817V) and, in the case of *KIT*F522C-associated SM, has been shown to be sensitive to imatinib therapy [29,45].

In the presence of blood eosinophilia, screening for *FIP1L1-PDGFRA*, using either FISH or RT-PCR, is warranted [16]. In contrast, conventional cytogenetics analysis generally permits identification of cases of BM mastocytosis associated with a *PDGFRB* rearrangement (i.e., chromosomal translocations involving 5q31-32) [18]. These cases with *PDGFRA/PDGFRB*-rearranged MPN with BM MC hyperplasia are appropriately classified as "Myeloid or lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* or *FGFR1*" per the WHO classification [10].

Risk Stratification

This section focuses on adult SM patients; their life expectancy, when considered as a group, appears to be shorter as compared to age- and gender-matched controls, with the excess deaths in this group occurring within the first 3–5 years after diagnosis (Fig. 4A) [9,71].

The categorization of adult SM patients per the 2008 WHO classification system remains the most practical first step in risk stratifying newly diagnosed patients [1]. The WHO classification recognizes seven mastocytosis categories (Table I) SM is sub-classified into four sub-categories: indolent SM (ISM; no evidence of extra-cutaneous organ dysfunction), aggressive SM (ASM; presence of extra-cutaneous organ dysfunction), SM associated with another clonal hematological non-MC lineage disease (SM-AHNMD), and mast cell leukemia (MCL).

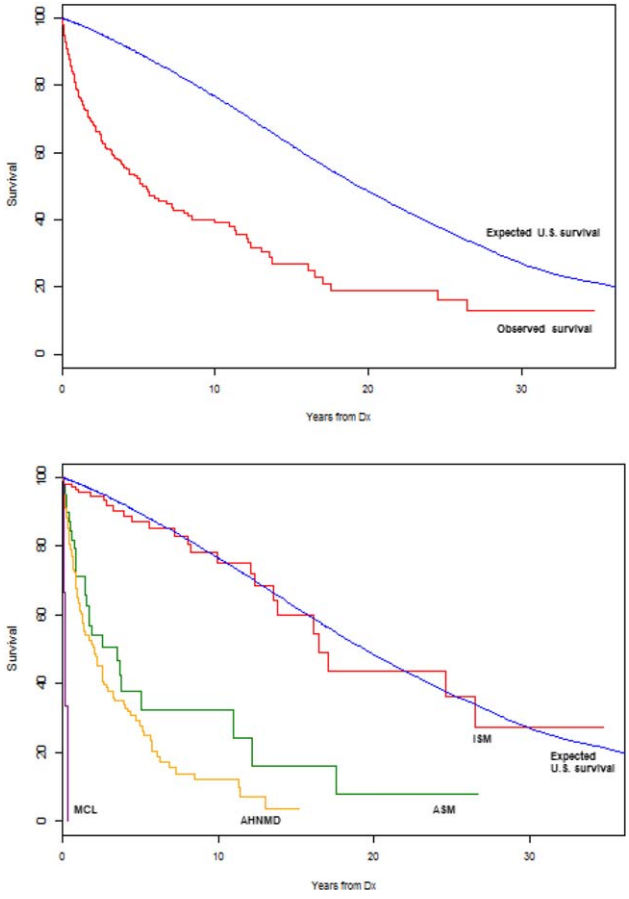

Figure 4. (a) The observed Kaplan-Meier survival for systemic mastocytosis patients (red) compared with the expected age and gender matched US population's survival (blue). (b) The observed Kaplan-Meier survival for systemic mastocytosis patients classified by disease type ISM (red), ASM (green), AHNMD (yellow) and MCL (purple) compared with the expected age and gender matched US population's survival (blue) for the entire cohort. (adapted from Ref. [9]).

A study of 342 adult patients has validated the prognostic value of the WHO classification for SM [9].

Indolent SM

Comprised the largest subgroup ($n = 159$; 46%) [9]. Compared to patients with ASM and SM-AHNMD, ISM patients were significantly younger at presentation (median age 49 years) and had a higher prevalence (66–75%) of UP-like skin lesions, MCMRS and gastrointestinal symptoms; ISM patients were significantly less likely however to exhibit constitutional symptoms or hepatosplenomegaly (<20%).

The WHO system recognizes two provisional ISM sub-variants: smoldering SM (SSM) and isolated bone marrow (BM) mastocytosis (BMM) [1]. SSM is characterized by a higher burden of MC defined by the presence of ≥2 'B-findings' (Tables I and II; Fig. 2). Of the 159 ISM patients in the aforementioned series, 22 (14%) had SSM, 36 (23%) BMM, and the remaining 101 (63%) did not fit in with either category (ISM-other) [54]. SSM patients were significantly older (median age 64 years) than patients with BMM or ISM-other and more frequently presented with constitutional symptoms (45%), anemia (55%) and elevated MC mediator levels. In contrast, BMM patients more frequently presented with MCMRS (86%), including anaphylaxis (78%). Overall median survival in ISM was 198 months, which was not significantly different than that of the age- and sex-matched U.S. control population (Fig. 4B, red curve). SSM patients had a significantly inferior survival (median 120 months) as compared to those with ISM-other (median 301 months) or BMM (not reached).

In a multivariable analysis, advanced age was the primary determinant of inferior survival and accounted for the marked difference in survival between SSM and the other two groups. The overall risk of transformation to acute leukemia or ASM was low (<1% and 3%, respectively) but was significantly higher in SSM (18%). Another recent study confirmed the low-rate of disease progression in ISM; after a median follow up of 147 months (range 61-329), the progression rate was 3%; predictors of disease progression were serum β2-microglobulin level and multilineage presence of *KIT*D816V [72].

Systemic mastocytosis with associated clonal hematological non-mast cell lineage disease

SM-AHNMD was the second most common SM subgroup ($n = 138$; 40%) in the aforementioned series [9,22]. Of these, 123 (89%) had an associated myeloid neoplasm, while the remainder had lymphoma ($n = 7$), myeloma ($n = 5$), chronic lymphocytic leukemia ($n = 2$), or primary amyloidosis ($n = 1$). Of the patients with an associated myeloid malignancy, 55 (45%) had SM-MPN, 36 (29%) SM-chronic myelomonocytic leukemia (SM-CMML) and 28 (23%) SM-MDS. A significant proportion ($n = 42$; 34%) exhibited prominent eosinophilia ($\geq 1.5 \times 10^9$/L), especially those with SM-MPN ($n = 31$; 56%); of the latter, 12 (39%) harbored the *FIP1L1-PDGFRA* fusion.

Overall median survival in SM-AHNMD was 24 months (Fig. 4B, gold curve). SM-MPN patients had a significantly longer median survival (31 months) as compared to patients with SM-CMML (15 months), SM-MDS (13 months), or SM-AL (11 months). Leukemic transformation (13% overall) was seen significantly more frequently in SM-MDS (29%), as compared to SM-MPN (11%) or SM-CMML (6%). Clinical outcome was similar between SM-MPN patients with or without eosinophilia.

Aggressive systemic mastocytosis

ASM was the third most common subgroup ($n = 41$; 12%) in the aforementioned series [9]. ASM patients frequently displayed constitutional symptoms (60%), hepatosplenomegaly (50%), lymphadenopathy (30%), severe anemia (Hgb <10 g/dL; 24%) or thrombocytopenia (platelets $<100 \times 10^9$/L; 27%), leukocytosis (41%), and markedly elevated serum tryptase levels (>200 ng/mL; 40%). Overall median survival in ASM was 41 months (Fig. 4B, green curve) and leukemic transformation occurred in two patients (5%).

Mast cell leukemia

MCL was relatively rare ($n = 4$; 1%) in the aforementioned series [9]; the prognosis in these cases was dismal with median survival of only 2 months (Fig. 4B, violet curve).

In addition to WHO SM subtype, multivariable analysis shown a significant and independent association between inferior survival and advanced age ($P < 0.0001$), history of weight loss ($P = 0.01$), anemia ($P = 0.007$), thrombocytopenia ($P = 0.0008$), hypoalbuminemia ($P = 0.0008$), and excess BM blasts (>5%; $P = 0.004$) [9].

A recent study showed increased plasma IL-2Rα/CD25 levels to be associated with inferior overall survival in advanced and indolent SM patients, independent of conventional risk factors [73].

*KIT*D816V, which is the hallmark of adult SM, has been shown to occur in BM hematopoietic cell compartments other than MC, particularly in cases of SM-AHNMD, ASM and MCL, but less frequently in ISM, thereby indicating involvement of a pluripotent stem cell in such cases [29]. Further, comprehensive immunophenotyping has shown that an immature BM MC phenotype ($CD25^+$/$Fc\epsilon RI^{lo}$/FSC^{lo}/SSC^{lo}/$CD45^{lo}$), in the absence of coexisting normal MC in the BM, correlated with multilineage hematopoietic involvement by

 doi:10.1002/ajh.24553

*KIT*D816V, regardless of the WHO SM subtype [74]. In contrast, BM MC from patients with ISM subtypes displayed a mature activated MC phenotype (e.g., increased expression of MC activation markers CD63, CD69 and CD203c in patients with BMM) [75]. While such assays require considerable technical expertise, and consequently are not routinely available, these data indicate the prognostic value of the aforementioned observations; in one study, multilineage *KIT*D816V involvement was the most important prognostic criterion for progression of ISM to more aggressive SM subtypes [72].

Recent data suggests that assessing the molecular profile of advanced systemic mastocytosis patients will be useful in establishing prognosis. In this regard, *ASXL1*, *RUNX1* and *SRSF2* mutations that are frequently observed in other myeloid malignancies have been identified as being prognostically detrimental [76,77]. A mutation-augmented prognostic scoring system (MAPSS) based on 5 parameters, namely age >60 years, hemoglobin <10 g/dL or red cell transfusion-dependence, platelet count $<150 \times 10^9$/L, serum albumin <3.5 g/dL, and ASXL1 mutation stratified advanced SM patients into high-, intermediate-, and low-risk groups with median survival of 5, 21, and 86 months, respectively ($P<0.0001$) [76].

Treatment

While treatment of adult SM is highly individualized, it is guided only to a limited extent by the presence or absence of a particular molecular abnormality. In general, treatment with small-molecule kinase inhibitors has yielded only modest clinical benefits, likely due to yet unrecognized complexities in the molecular pathogenesis of SM, redundancies in cellular signaling pathways and/or ineffectiveness of currently available in vivo KITD816V-inhibitors. For the rare SM patient with a transmembrane KIT mutation (e.g., F522C or K509I), dramatic clinical responses to imatinib therapy can be observed [43,45]. Overall however, although significant progress has been achieved with some of the newer investigational agents (e.g., midostaurin/PKC412) [78], the promise of truly 'targeted therapy' in the vast majority of SM patients (akin to imatinib therapy in CML) has yet to be realized. Drug therapy has not been shown to favorably affect survival in SM and the experience with allogeneic stem cell transplantation remains limited [79,80]. Current therapy in WHO-defined SM is largely palliative and directed at MC degranulation symptoms (e.g., pruritus, urticaria, angioedema, flushing, nausea, vomiting, abdominal pain, diarrhea, episodic anaphylactoid attacks) (Table III), symptomatic skin disease (e.g., urticaria pigmentosa) and/or organ dysfunction from MC tissue infiltration (e.g., hypersplenism or pathologic fracture). Treatment options in SM range from observation alone (supplemented by preventative measures to avoid precipitating MCMRS), to symptom management (e.g., managing pruritus or diarrhea), to supportive measures (e.g., red blood cell transfusion or osteoporosis treatment), to cytoreductive therapy for MC debulking in the setting of aggressive, advanced, or treatment-refractory disease. Results from a retrospective study of SM patients who underwent allogeneic stem cell transplantation (ASCT) were recently reported; of a total 57 patients (median age 46 years), 38 had SM-AHNMD (20 with AML), 12 MCL and 7 ASM [80]. The primary assessment of treatment response was at day +100 post-ASCT; 16 patients (28%) achieved complete remission of the mastocytosis component with two patients becoming *KIT*D816V-negative. Another 24 (42%) and 12 patients (21%) had partial response and stable disease, respectively; primary refractoriness was chiefly observed in MCL patients. The associated hematological malignancy was more treatment sensitive, with complete remission of this component being noted in all 38 SM-AHNMD patients. Overall survival at 3 years was 55% for the entire cohort, and 74% for the SM-AHNMD subgroup. Predictors of poor overall survival were presence of MCL (versus ASM or SM-AHNMD), reduced-intensity (versus myeloablative) conditioning and disease-progression (versus response or stable disease). A consensus opinion on ASCT in advanced systemic mastocytosis has recently been published [81]. Recently published consensus criteria will also facilitate objective and standardized assessment of treatment response in patients with advanced SM in the era of novel, molecularly targeted drugs [82].

Currently used agents for SM therapy are presented below. Our current algorithm for SM treatment is illustrated in Fig. 5.

Interferon (IFN)-α

IFN-α is often considered the first-line cytoreductive therapy in symptomatic SM; since the initial report in 1992 [83], several case reports or small series have shown IFN-α (IFN-α2b in most instances) to improve symptoms of MC degranulation, decrease bone marrow MC infiltration, and ameliorate mastocytosis-related ascites/hepatosplenomegaly, cytopenias, skin findings, and osteoporosis [84–96]. IFN-α treatment is not uniformly effective [97], and the frequency of major response (i.e., complete resolution of one or more baseline 'C' findings) is approximately 20–30%; the optimal dose and duration of IFN-α therapy for SM remain unclear, however concurrent administration of corticosteroids (prednisone) may improve its efficacy (up to 40% major response rate) and tolerability [91,98]. The time to best response may be a year or longer [91] and delayed responses to therapy have been described [99]. IFN-α treatment is frequently (up to 50%) complicated by toxicities, including flu-like symptoms, bone pain, fever, cytopenias, depression, and hypothyroidism; consequently, the adverse dropout rate with IFN-α treatment is not trivial [91,100,101]. Finally, a significant proportion of patients will relapse within a short period of IFN-α treatment being discontinued, illustrating the cytostatic rather than cytolytic effects of the drug [101].

In a French study, 20 SM patients (16 ASM and 4 ISM) were treated with IFN-α starting at 1 MU/day with progressive increase to 5 MU/m^2/day; 13 patients were treated for at least 6 months (median dose 3.2 MU/day) [101]. All 13 patients exhibited responses (non were complete) in systemic and cutaneous disease manifestations that were associated with decrease in circulating MC mediator levels, but not in BM MC burden. Adverse effects were frequent (cytopenias and depression in nine and seven patients, respectively); there were two deaths during the treatment phase. Four responding patients experienced prompt relapse of symptoms after treatment cessation.

In the Mayo Clinic study, 47 patients received IFN-α with or without prednisone [100]; the median weekly dose was 15 MU per week (range 3.5–30 MU per week) and the initial dose of prednisone ranged from 20 to 60 mg per day with a slow tapering over weeks or months in some patients. In 40 evaluable patients, the overall response rate (ORR) was 53% (ISM and ASM 60%; SM-AHNMD 45%). Overall median duration of response was 12 months (range, 1–67 months). Responses were not significantly different when comparing patients who did and did not receive prednisone. Absence of systemic mediator-related symptoms was significantly associated with inferior response to IFN-α; 41% vs. 77%, respectively. Major toxicities included fatigue, depression and thrombocytopenia.

Summary

IFN-α has activity in all SM subcategories and has been shown to improve dermatological, hematological, gastrointestinal, and systemic symptoms associated with histamine release. IFN-α also has a role in treating skeletal symptoms because of its ability to increase bone density. Use of higher doses of IFN-α has the potential to decrease the BM MC burden in some patients. We commonly start treatment at the dose of 1–3 million units (MU) subcutaneously three times per

week, followed by gradual escalation to 3–5 MU three to five times per week, if tolerated. Prednisone (30–60 mg/day) is commonly added at the start of treatment to improve tolerability and response, and is tapered over a 2–3 month period. IFN-α treatment is generally continued as long as a response is observed and there are no intolerable adverse effects.

TABLE III. Pharmacologic Therapies for Symptom Control in *Adult* Patients with Indolent Systemic Mastocytosis (Adapted from Ref. [53])

Symptoms	Treatment ladder[b]	Drug class	Specific drugs/doses	Common side effects (>5-10%)/ Precautions[c]
Pruritus/flushing	1st-line	H1-antagonist	Cetirizine 5-10 mg/d* Fexofenadine 60mg BID or 180 mg/d* Hydroxyzine 25mg q 6h* *Doses can be increased with supervision if indicated	Headache, somnolence, confusion, asthenia, xerostomia ***Precautions***: *Hydroxyzine* -anticholinergic effects: use with caution in older patients, those with glaucoma, BPH, asthma, etc.
	2nd-line	Leukotriene antagonist	Montelukast 10 mg/d Zafirlukast 20 mg BID	Headache ***Precautions***: liver function impairment, neuropsychiatric conditions
	3rd-line	Non-steroidal anti-inflammatory drug	Aspirin (*see text*)	Gastrointestinal bleeding, peptic ulcer disease ***Precautions***: May precipitate anaphylactic reaction (*see text*), aspirin hypersensitivity, children/adolescents with flu (Reye's syndrome), hepatic or renal dysfunction, bleeding disorders
	3rd-line	Psolaren plus ultraviolet A (PUVA) photochemotherapy	See specialized texts	Nausea, pruritus, erythema of varying degree, increased risk of non-melanoma skin cancers. ***Contraindications***: Pregnancy, xeroderma pigmentosa, lupus erythematosus with photosensitivity
Abdominal pain, cramping, diarrhea, heartburn, nausea, vomiting	1st-line	H2-antagonist	Ranitidine 150 mg BID Famotidine 10 mg BID Cimetidine 400 mg BID	Headache, abdominal pain, dizziness, constipation, diarrhea *Cimetidine*: gynecomastia
	2nd-line	Proton pump inhibitor	Omeprazole 20 mg/d Pantoprazole 40 mg/d Rabeprazole 20 mg/d	Headache, abdominal pain, nausea, vomiting, diarrhea, flatulence
	3rd-line	Sodium cromolyn	100–200 mg QID 30 minutes before meals and bedtime	Dysgeusia, cough, osmotic diarrhea
	4th-line	Corticosteroid	Prednisone 0.5–1 mg/kg/d starting dose; taper as feasible based on response/ tolerance	Dose/duration dependent (consult comprehensive drug reference resource)
Headache, cognitive impairment, depression	1st-line	H1- *and* H2-antagonist	As above	As above
	2nd-line	Sodium cromolyn	As above	As above
Recurrent hypotension[a]	1st-line	Epinephrine	See text	See text
	2nd-line	H1- *and* H2-antagonists	As above	As above
	3rd-line	Corticosteroid	Prednisone (as above)	As above
	4th-line	Cytoreductive therapy (Interferon-α or 2-chlorodeoxyadenosine)	See text/below	See text/below
Osteoporosis	1st-line	Bisphosphonate	Alendronate 70 mg q week Risedronate 35 mg q week Pamidronic acid 90 mg IV q 4 weeks Zolendronic acid 4 mg IV q 4 weeks	Flu-like symptoms, abdominal pain, nausea, vomiting, diarrhea, asthenia, hypocalcemia, rash musculoskeletal pain, headache, osteonecrosis of the jaw, nephrotoxicity. Follow established guidelines for bisphosphonate use (*see text*) ***Precautions***: esophageal/upper GI disease (*oral bisphosphonates*), renal disease, poor oral hygiene or dental procedures
	2nd-line	Cytokine/ Immunomodulatory drug	Interferon-α Starting dose: 1–3 MU SQ three times per week Target dose: 3–5 MU SQ 3–5 times per week	Dose dependent (consult comprehensive drug reference resource) ***Comment***: pegylated interferon may be better tolerated

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TABLE III. *Continued*

Symptoms	Treatment ladder[b]	Drug class	Specific drugs/doses	Common side effects (>5-10%)/ Precautions[c]
	3rd-line	Purine nucleoside analogue	2-Chlorodeoxyadenosine (Cladribine/2-CdA) Dose: 5 mg/m[2] IV × 5 days every 4–8 weeks	Myelosuppression, immunosuppression

[a] Avoidance of symptom trigger(s) applies to all patients. Those at risk of anaphylaxis should carry an emergency kit with self-injected epinephrine (EpiPen) (*see text*). Immunotherapy can be considered in those with IgE-mediated allergic reactions (*see text*).
[b] Treatments can be combined in a stepwise manner for inadequate symptom control at prior step if clinically indicated/feasible.
[c] Basic overview provided. Consult a comprehensive drug reference manual for detailed information regarding feasibility of use during pregnancy, black box warnings, specific contraindications/precautions, drug-drug interactions, dose reduction for hepatic/renal dysfunction, etc.
H1- and H2- indicate histamine receptor 1 and 2, respectively; mg, milligram; d, day; QD, once daily; BID, twice a day; QID, four times a day; BPH, benign prostatic hypertrophy; kg, kilogram; q, every; MU, million units; GI, gastrointestinal; SQ, subcutaneously; and IV, intravenously.

2-chlorodeoxyadenosine (cladribine or 2-CdA)

2-chlorodeoxyadenosine (cladribine or 2-CdA) has demonstrated in vitro and in vivo activity against neoplastic MC; the published experience suggests that 2-CdA has therapeutic activity in all SM subtypes including in MCL [102–107].

In the Mayo Clinic study, 2-CdA was administered to 26 patients (8 as first-line); the dose was 5 mg/m^2 per day or 0.13–0.17 mg/kg per day for 5 days as a 2-hour intravenous (IV) infusion, and median number of treatment cycles was 3 (range 1 to 9) [100]. Treatment response was evaluable in 22 patients and the ORR was 55% (ORR in ISM, ASM, and SM-AHNMD was 56%, 50%, and 55%, respectively). Median duration of response was 11 months (range, 3–74 months). Presence of circulating immature myeloid cells was significantly associated with inferior response to 2-CdA (0% vs. 75%). Major toxicities were myelosuppression and infection.

In a recent French study, 44 patients with mastocytosis were treated with 2-CdA (CM = 3, ISM = 19, SSM = 3, ASM = 12, SM-AHNMD = 6 and MCL = 1) [108]. All patients had failed previous symptomatic therapy and/or IFN-α ($n = 10$) or kinase inhibitors ($n = 7$). 2-CdA was given at 0.15 mg/kg/day in a 2-hour infusion or subcutaneously for 5 days, repeated every 1–2 months, for a median of 4 cycles. After a median follow up of 35 months, no opportunistic infections were seen with the exception of zoster infection in two patients. Responses occurred in 24/31 patients with urticaria pigmentosa, 17/35 with fatigue, 14/24 with flushing, 9/24 with pruritus, 9/21 with abdominal pain, 1/9 with ascites, 11/23 with diarrhea, 8/16 with weight loss, 4/14 with headache, 5/10 with cough, 7/20 with

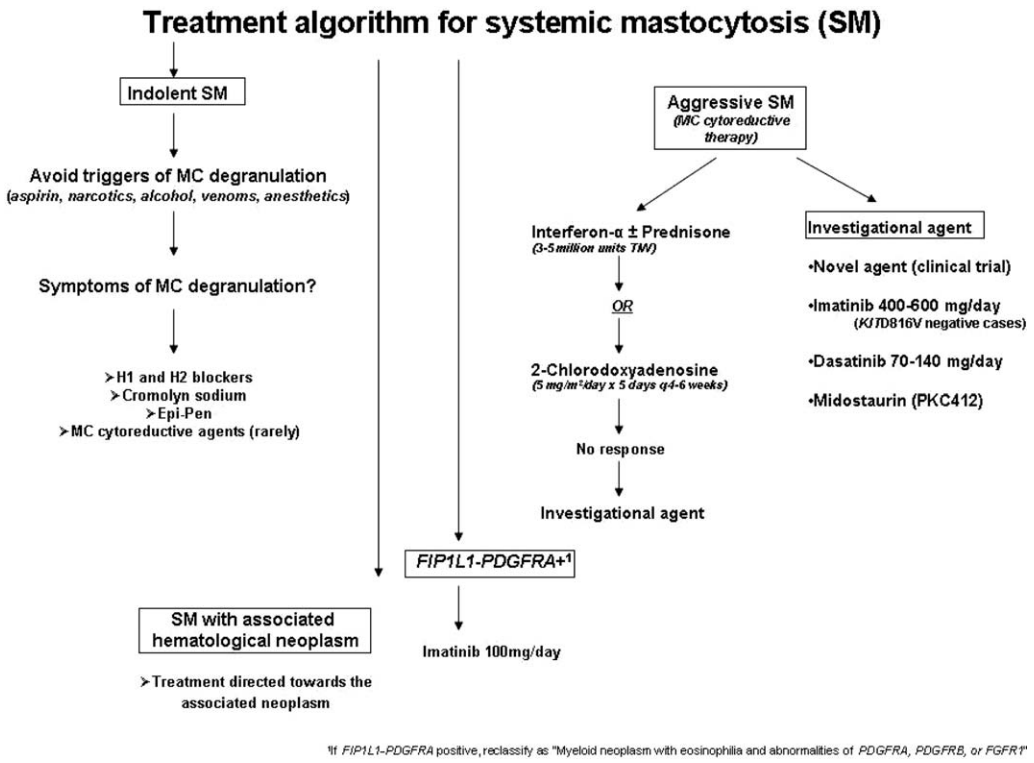

Figure 5. Algorithm for the treatment of systemic mastocytosis.

splenomegaly, 2/6 with lymphadenopathy, 0/2 with pleural effusions and 5/19 with neuropsychological symptoms. In addition, eosinophil count normalized in 7/10 cases and a substantial decrease in tryptase levels was also noted. Overall, major (MR) and partial (PR) responses were observed in 7/12 patients with ASM, 3/3 SSM, 17/19 ISM, 2/3 CM but in none of the patients with SM-AHNMD. Median duration of response was approximately 20 months.

Summary

2-CdA has activity in all SM subtypes. We use 2-CdA as first-line treatment in cases where rapid MC debulking is indicated, or in symptomatic patients who are refractory or intolerant to IFN-α. Potential toxicities of 2-CdA include myelosuppression and lymphopenia with increased risk of opportunistic infections. The limited activity of 2-CdA in SM-AHNMD patients noted in the French study is discrepant with published data; the discrepancy may relate to alternative interpretation of the treatment response data and needs to be confirmed.

Imatinib mesylate (IM)

demonstrates in vitro efficacy against wild-type KIT and certain trans-membrane (F522C) and juxta-membrane (V560G) KIT mutants, but not the common kinase (D816V) domain mutants [45,109–111]. Similarly, not all juxta-membrane mutations may be sensitive to IM (e.g., V559I) [112].

In the Mayo Clinic study that excluded *FIP1L1-PDGFRA*-positive cases, IM was administered to 27 SM patients; the median starting dose was 400 mg per day (range 100-400 mg/day), and the maintenance dose in responding patients ranged from 200 mg/day to 400 mg/day [100]. In 22 evaluable patients, the ORR was 18% (ORR in ISM, ASM, and SM-AHNMD was 14%, 50%, and 9%, respectively), and median duration of response was 19.6 months (range, 9–69 months). Responses included improvement in UP and decrease in the BM MC burden. The majority (86%) of IM treated patients were *KIT*D816V positive—ORR in mutation-positive and—negative patients was 17% and 33%, respectively. None of the 6 patients with SM and associated eosinophilia (all *KIT*D816V-positive) responded to IM treatment. Major toxicities included diarrhea and peripheral edema; two patients developed interstitial pneumonitis.

Data from another study however suggested an ORR of 36% in *KIT*D816V-positive SM patients [113]. In yet another study of 20 SM patients treated with IM, only one *KIT*D816V-negative patient responded while 6 other patients reported symptomatic improvement [114]. Finally, in another study wherein 17 SM patients received IM treatment, the response rate was 29% (1 complete and 4 partial remissions), all in *KIT*D816V-negative patients [115].

Summary

While IM is the only SM treatment currently approved by the Food and Drug Administration (FDA) (specific indication is treatment of adult patients with ASM without the KITD816V mutation or with unknown KIT mutational status), it has a limited role in the treatment of unselected SM patients, the majority of whom likely harbor KITD816V. The rare SM cases that harbor an IM-sensitive KIT mutation, or those that are KITD816-unmutated may be appropriate candidates for IM treatment.

Hydroxyurea (HU)

In the Mayo Clinic study, HU was given to 30 SM patients (28 with SM-AHNMD) [100]. The drug was used as first-line therapy in 24 patients. The dose ranged from 500 mg every other day to 2000 mg per day. Treatment response was evaluable in 26 patients; control of thrombocytosis, leukocytosis and/or hepatosplenomegaly was observed in 5 SM-AHNMD patients (ORR = 19%). Median duration of response was 31.5 months (range, 5–50 months) and the major toxicity was myelosuppression.

Summary

The utility of HU in treating SM-AHNMD stems from its myelosuppressive activity. HU does not however exhibit any substantial anti-MC effect.

Investigational agents

Dasatinib. Dasatinib has shown efficacy in vitro against various KIT mutants including D816V [116,117]. Furthermore, dasatinib may synergize with PKC412 and chemotherapy in this regard [118–120]. In the largest study of dasatinib therapy in SM [121], the drug was given at a starting dose of 70 mg PO bid to 33 SM patients:18 ISM, 9 ASM and 6 with SM-AHNMD. Two (6%) patients, both of whom were D816V-negative, achieved complete remission. Nine (27%) patients experienced symptomatic improvement. Grade 3 toxicities were observed in 19 (58%) patients. In another report [122], 4 SM patients (all KITD816V positive; 2 with ASM, 1 SM-AHNMD, and 1 ISM) were treated with dasatinib at a dose ranging from 50mg to 100 mg twice daily. Two patients (1 each with ASM and SM-AHNMD) had a major response, which in the case of the SM-AHNMD patient was accompanied by decrease in the BM MC burden. Both responders experienced an initial exacerbation of MCMRS and rash lasting several days before the benefits of dasatinib therapy became evident.

Summary. Dasatinib appears to have modest activity in KITD816V-positive SM. The cumulative published experience to date does not clarify as to which group of SM patients is likely to obtain the most benefit from dasatinib therapy.

Midostaurin (PKC412). Midostaurin (PKC412) has in vitro activity against kinase domain KIT mutants (D816Y and D816V) [103,123], and treatment of a patient with MCL who harbored KITD816V resulted in transient clinical benefit [124]. In the global Phase 2 CPKC412D2201 trial, 116 patients with advanced SM were enrolled; the primary efficacy population comprised of 89 patients (16 with ASM, 57 with SM-AHNMD, and 16 with MCL); patients were treated with PKC412 at 100 mg BID [78].The overall response rate per conventional criteria was 60% with 45% having a major response and 15% having a partial response. The response rate was 75% in ASM patients, 58% in SM-AHNMD patients and 50% in MCL patients. After a median follow up of 26 months (range 12–54), the median duration of response was not reached in ASM or MCL patients and was 12.7 months in SM-AHNMD patients. Responses occurred regardless of KITD816V status. Reversal of organ damage (major or partial responses) was reflected by normalization of hypoalbuminemia (58%), achieving red blood cell transfusion independence (40%) or platelet transfusion independence (100%), improvement in liver function test abnormalities (44–58%), and/or reversion of weight loss (25%). Patients reported improvement of disease-related symptoms with treatment. The median overall survival for ASM, SM-AHNMD and MCL subgroups was not reached, 20.7 months and 9.4 months, respectively. The corresponding progression free survival for the 3 groups was 28.7 months, 11 months, and 11.3 months, respectively. In a post hoc analysis, the median overall survival was significantly longer among patients who had a response than among those who did not have a response (44.4 months vs. 15.4 months; hazard ratio for death, 0.42; $P = 0.005$). Outcomes that were associated with longer overall survival were response versus nonresponse (hazard ratio, 0.44; $P = 0.03$) and a decrease in bone marrow mast cell burden of 50% or more versus less than 50% (hazard ratio, 0.33; $P = 0.01$). Of 72 patients who could be evaluated for response, 41 (57%) had a decrease in bone marrow mast-cell burden of 50% or more.

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The median best percentage change in bone marrow mast-cell burden was −59% (range, −96 to 160). The median best percentage change in serum tryptase level was −58% (range, −99 to 185); 53 of 89 patients (60%) had a decrease of more than 50%.

Of the 116 patients in the intention-to-treat population, 72% had discontinued treatment (33% and 22% due to disease progression and adverse events, respectively).The most common drug side effects (all grades/grades 3–4) were nausea (79%/6%), vomiting (66%/6%), diarrhea (54%/3%) and fatigue (28%/9%). New or worsening grade 3 or 4 neutropenia, anemia, and thrombocytopenia occurred in 24%, 41%, and 29% of patients, respectively; many of these patients had pre existing cytopenias. The dose of midostaurin was reduced in 65 patients (56%), mostly due to adverse events (in 48 patients). Re-escalation to the initial dose level was accomplished in 21 of the 65 patients (32%).

Summary. Midostaurin is highly efficacious for the treatment of advanced SM and produces improvement in organ function with substantial reduction in MC burden in most patients. Response to midostaurin treatment was associated with a decrease in the risk of death, particularly in mast cell leukemia patients. However, it is currently not clear whether patients with SM-AHNMD benefit from midostaurin as first-line treatment vis-à-vis treatment with IFN-α or cladribine or allogeneic stem cell transplantation.

Masatinib mesilate (AB1010). Masatinib mesilate (AB1010) has been shown to inhibit human and murine KIT with juxtamembrane activating KIT mutations, as well as PDGFRA-α/β, and Lyn kinases at nanomolar concentrations in cell-based assays [125]. In contrast, masatinib only weakly inhibited KITD816V-driven cell proliferation (micromolar concentrations). Masatinib was administered to 25 patients with symptomatic cutaneous or ISM that was refractory to conventional therapy, and where KITD816V was absent in at least one MC infiltrated organ (skin or BM) [126]. Patients were randomized to receive 3 or 6 mg/kg/day for 12 weeks; the primary endpoint was change in symptoms at week 12 relative to baseline. There was a significant improvement in frequency of flushing, pruritus score and Hamilton rating for depression by 64%, 36%, and 43%, respectively. The overall clinical response (≥50% improvement in baseline symptom without deterioration or emergence of another symptom) was 56%. Twenty two patients (88%) completed the study; 2 discontinued due to adverse events (AE). In the initial 12 week phase, 21 patients (84%) experienced at least one masatinib-related AE (mild [n = 11], moderate [n = 19] and severe [n = 9]). The most common AE were nausea/vomiting (52%), edema (44%), muscle spasms (28%) and rash (28%). One patient developed masatinib-related agranulocytosis that was reversible. Seventeen patients (68%) entered the extension phase and at the time of publication, 8 patients (32%) were still receiving treatment. In another report of 35 ISM patients (22 and 2 patients with mild-moderate and severe depression, respectively), depression scores were significantly improved (20% improvement in initial score) in 67% of cases after masatinib therapy for 12 weeks [127].

Summary. Given its lack of activity against KITD816V, masatinib appears to be at a disadvantage as compared to other 'targeted' therapies for the treatment of adult SM. In the absence of a head-to-head trial, it is unclear if masatinib has any clear advantage over imatinib for the treatment of symptomatic ISM. The frequency of AE in the former study was relatively high, which likely explains why the QLQ-C30 symptom score showed little improvement as compared to baseline.

Brentuximab vedotin. Brentuximab vedotin is an antibody-drug conjugate directed against the cell-membrane protein CD30, which a member of the tumor necrosis factor receptor superfamily. Given the reported aberrant expression of CD30 on neoplastic MC, with preferential expression in advanced SM as compared to ISM (see above) [59], the role of brentuximab vedotin in treating advanced SM including MCL is being currently studied (Clinicaltrials.gov study# NCT01807598). In a preliminary report, two of four SM patients treated with brentuximab had a response [128].

BLU-285. BLU-285 is a small molecule kinase inhibitor that selectively inhibits exon 17 mutants of KIT, including KITD816V, at nanomolar concentrations [129,130]. BLU-285 also inhibits the analogous mutation in PDGFRA, namely D842V, seen in imatinib-refractory gastrointestinal stromal tumors (GIST). The compound has shown therapeutic activity in murine models of mastocytosis, and a Phase 1 open label dose escalation study is currently underway in patients with advanced SM and relapsed or refractory myeloid malignancies (Clinicaltrials.gov study# NCT02561988).

DCC-2618. DCC-2618 is a Type II switch pocket control inhibitor which potently inhibits exon 17 KIT mutations that are resistant to conventional kinase inhibitors [131]. An ongoing Phase 1 open label dose escalation study is examining the safety and tolerability of DCC-2618 in patients with advanced malignancies including ASM and MCL (Clinicaltrials.gov study# NCT02571036).

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