Clinical Management Review

Personalized Management Strategies in Mast Cell Disorders: ECNM-AIM User's Guide for Daily Clinical Practice

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Mastocytosis is a myeloid neoplasm defined by expansion and focal accumulation of clonal mast cells (MCs) in one or more organs. The disease exhibits a complex pathology and may be complicated by MC activation, bone abnormalities, neurological problems, gastrointestinal symptoms, and/or hematologic progression. The World Health Organization divides mastocytosis into cutaneous forms, systemic mastocytosis (SM) and MC sarcoma. In most patients with SM, somatic mutations in *KIT* are detected. Patients with indolent SM have a normal to near-normal life expectancy, whereas patients with advanced SM, including aggressive SM and MC leukemia, have a poor prognosis. In those with advanced SM, multiple somatic mutations and an associated hematologic neoplasm may be detected. Mediator-related symptoms can occur in any type of mastocytosis. Symptoms may be mild, severe, or even life-threatening. In patients with severe acute symptoms, an MC activation syndrome may be diagnosed. In these patients, relevant comorbidities include IgE-dependent and

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Abbreviations used

AHN- *associated hematologic neoplasm*
AIM- *American Initiative in Mast Cell Diseases*
AML- *acute myeloid leukemia*
ASM- *aggressive SM*
BM- *bone marrow*
BMM- *BM mastocytosis*
CM- *cutaneous mastocytosis*
ECNM- *European Competence Network on Mastocytosis*
GPSM-OS- *Global Prognostic Score for SM optimized for Overall Survival*
GPSM-PFS- *GPSM optimized for Progression-Free Survival*
HαT- *hereditary alpha tryptasemia*
HR- *histamine receptor*
IPSM- *International Prognostic Score for Mastocytosis*
ISM- *indolent SM*
MARS- *Mutation-Adjusted Risk Score*
MC- *mast cell*
MCAS- *MC activation syndrome*
MCL- *MC leukemia*
MCS- *MC sarcoma*
RANKL- *receptor activator of nuclear factor kappa beta*
SM- *systemic mastocytosis*
SM-AHN- *SM with an associated hematologic neoplasm*
SSM- *smoldering SM*
WHO- *World Health Organization*

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IgE-independent allergies. Management of patients with SM is an emerging challenge in daily practice and requires in-depth knowledge and a multidisciplinary and personalized approach with selection of appropriate procedures and interventions. In this article, we review the current knowledge on SM and MC activation syndrome, with emphasis on multidisciplinary aspects in diagnosis and patient-specific management. In addition, we provide a user's guide for application of markers, algorithms, prognostic scores, and treatments for use in daily practice. © 2022 The Authors. **Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/). (J Allergy Clin Immunol Pract 2022;10:1999-2012)**

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INTRODUCTION

Mast cells (MCs) are tissue-resident immune cells involved in a diversity of physiologic and pathologic reactions in health and disease.[1-6] MCs exhibit a number of activation-linked surface antigens, including high-affinity receptors for IgE.[1-6] MCs also produce proinflammatory and vasoactive mediators, several of which are stored within cytoplasmic metachromatic granules.[1-6] During an anaphylactic reaction, MC activation is associated with both the rapid generation of arachidonic metabolites and immediate release of preformed, granule-derived mediators.[1-6]

MC disorders include (1) MC hyperplasia, defined by expansion of nonclonal MCs; (2) mastocytosis (clonal disease of MCs), (3) myelomastocytic leukemia, an extremely rare malignancy; and (4) MC activation disorders, including MC activation

syndromes (MCASs) (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).[2,6-15] Based on World Health Organization (WHO) criteria, mastocytosis is classified into cutaneous mastocytosis (CM), systemic mastocytosis (SM), and MC sarcoma (MCS).[7-11,14-16] Although diagnostic criteria for each of these conditions have been established and recommendations for diagnosis and management are available,[7-17] there remain ongoing discussions about diagnostic algorithms, prognostication, and optimal management. In fact, over recent years, a number of novel disease-related and patient-related prognostic factors have been identified.[16-26] In addition, predisposing factors and critical comorbidities have been defined and several prognostic scoring systems established.[18-29] A critical point is that in a number of patients, 2 or even 3 MC-involving pathologies may be detected, which potentially act together to initiate or aggravate symptoms in these patients.[30-33]

In this article, we include an overview of new diagnostic markers and therapeutic concepts in MC disorders, with special emphasis on multidisciplinary aspects and challenges. In addition, we provide a user's guide for application of biomarkers, diagnostic algorithms, and disease management strategies in routine medical practice. Our proposed recommendations focus on adult patients and were developed by a consortium of experts from the European Competence Network on Mastocytosis (ECNM) and the American Initiative in Mast Cell Diseases (AIM).

APPROACH TO PATIENTS WITH SUSPECTED SM AND/OR MCAS: INITIAL SCREEN

Initial clinical assessment includes a detailed case history and precise physical examination, including an inspection of the skin.[7,10,31,34] Typical maculopapular skin lesions with a positive Darier's sign are a strong indication for the presence of mastocytosis, which is usually confirmed by histology.[34] Unlike in children, in whom the diagnosis is usually CM, most adult patients are diagnosed with SM.[7,10,34-36] Therefore, the presence of characteristic skin lesions in adults often leads to the assumption that the patient has SM. However, it is important to distinguish between adult CM and SM in these cases, because the prognosis of adulthood CM is better than that of SM regarding event-free and overall survival.[27,35] Therefore, a detailed examination of the bone marrow (BM) is recommended for all adult patients to confirm or eliminate the diagnosis of SM and to initiate prognostication.[7-10,13-17]

If no BM examination has been performed or BM studies are delayed in adults, the resulting provisional diagnosis is "mastocytosis in the skin" (MIS).[10,13,35] It is important to inform these patients about differential diagnoses (CM vs SM), clinical implications, prognosis, and management. Patients with mastocytosis in the skin should have a scoring system evaluation to estimate the likelihood of SM.[37] The score commonly applied in these cases (ECNM or Fuchs score[37]) and a guide for its application and practical use are presented in Figure 1.

When no skin lesions are detected, other clinical and laboratory findings may support the diagnosis of SM.[7-10,15-17,38] These include unexplained osteoporosis, anaphylaxis, histamine-induced symptoms (cramping, headache, hypotension, diarrhea), blood cell count abnormalities (eg, cytopenia and eosinophilia), and splenomegaly.[7-10,15-17,38] In all patients, basal serum tryptase levels should be determined and blood leukocytes
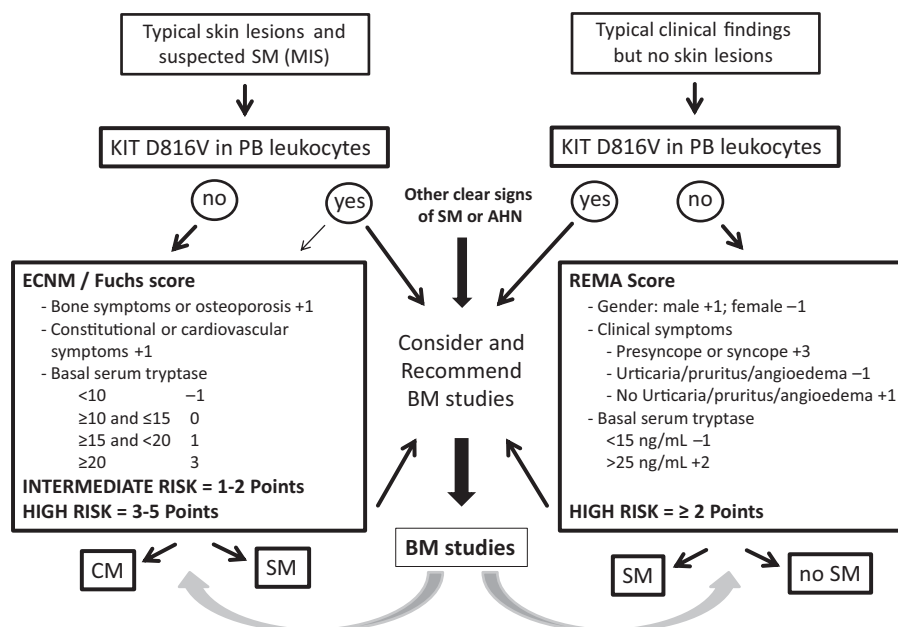
FIGURE 1. Basic algorithm for patients with suspected SM. In adult patients with typical skin lesions, a BM examination should be performed to confirm or exclude CM and SM. When the BM analysis is not performed or delayed, the provisional diagnosis is "mastocytosis in the skin" (MIS). In these patients, peripheral blood leukocytes are examined for *KIT* p.D816V and the basal serum tryptase level is determined. When *KIT* p.D816V is detected, BM studies are performed. If this is not the case, the Fuchs score can be applied to determine the likelihood of SM. When no skin lesions are identified, but typical clinical signs and symptoms are found (right of figure), blood leukocytes are examined for *KIT* p.D816V. When *KIT* p.D816V is detectable, BM studies are recommended. Otherwise, the REMA score is applied and in "high-risk" patients, a BM examination is recommended. *PB*, Peripheral blood; *REMA*, Red Española de Mastocitosis.

examined for expression of *KIT* p.D816V using a highly sensitive allele-specific PCR test.[38,39] When a *KIT* mutation is detected and/or serum tryptase levels are markedly elevated (>30 ng/mL), a BM examination is recommended (Figure 2).[7-10,15,37-39] When no *KIT* mutation is detected and no other signs indicative of a hematologic neoplasm are found, but the serum tryptase level is elevated (>10 ng/mL), a droplet digital PCR test determining the copy numbers of the alpha tryptase (*TPSAB1*) gene should be performed if the test is available (Figure 2). When, in such a patient, the PCR test reveals an increased *TPSAB1* gene copy number and thus hereditary alpha tryptasemia (HαT), no BM examination is required, but follow-up is necessary because some of these patients may develop SM. Notably, the prevalence of HαT in patients with SM is rather high.[40,41] The REMA score[42,43] should also be applied in these patients, and may reveal a high risk of SM (Figures 1 and 2).[38]

The ECNM has proposed a diagnostic algorithm for patients with suspected SM.[38] An update of this algorithm is shown in Figure 2. In this revised version, HαT is included as a new, relevant biomarker. In particular, the absence of HαT in a patient with markedly elevated basal tryptase (>30 ng/mL) must lead to the working hypothesis that the patient has SM or another (myeloid) BM neoplasm. In these patients, a BM examination is recommended, even if no mutation in *KIT* is detected (Figure 2). Table I provides a compilation of clinical and laboratory features indicative of the presence of SM in diverse clinical contexts.

Figure 3 shows a diagnostic algorithm for patients with suspected MCAS. In these patients, the basal serum tryptase level as

well as an event-related tryptase level must be determined.[12,13,44,45] Many patients with MCAS exhibit typical clinical symptoms of anaphylaxis.[12,13] These symptoms are episodic and recurrent and involve more than 1 organ system (Figure 3; see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). A summary of typical clinical findings in patients with MCAS is presented in Table II. During the diagnostic workup for MCAS, potential triggering factors and screening parameters indicating the presence of an underlying disorder, such as SM or an IgE-dependent allergy, should be determined.[44,45] Specific items include a highly sensitive PCR test for the *KIT* p.D816V mutation in blood leukocytes, a droplet digital PCR test to determine the HαT carrier status if the test is available, and the measurement of total and antigen-specific IgE.[44,45] In addition, the patient should be evaluated for infections, hypersensitivity against foods, drugs, or other triggers, and signs and symptoms indicative of the presence of allergic/atopic diseases or reactive disease processes.[44,45] In general, we recommend the use of the guidelines and diagnostic algorithm recently published by the EU/US (ECNM-AIM) consensus group.[44]

A confirmed allergy, SM, and/or a positive HαT test result increase the likelihood that the patient is suffering from MCAS when MCAS-like symptoms (especially anaphylaxis) are present. However, neither SM nor a positive HαT test result with an elevated basal tryptase is diagnostic of MCAS. Rather, carriers of HαT and patients with SM may be asymptomatic or suffer only from mild mediator-related symptoms.[44,45] The most important laboratory test in a patient with suspected MCAS is the
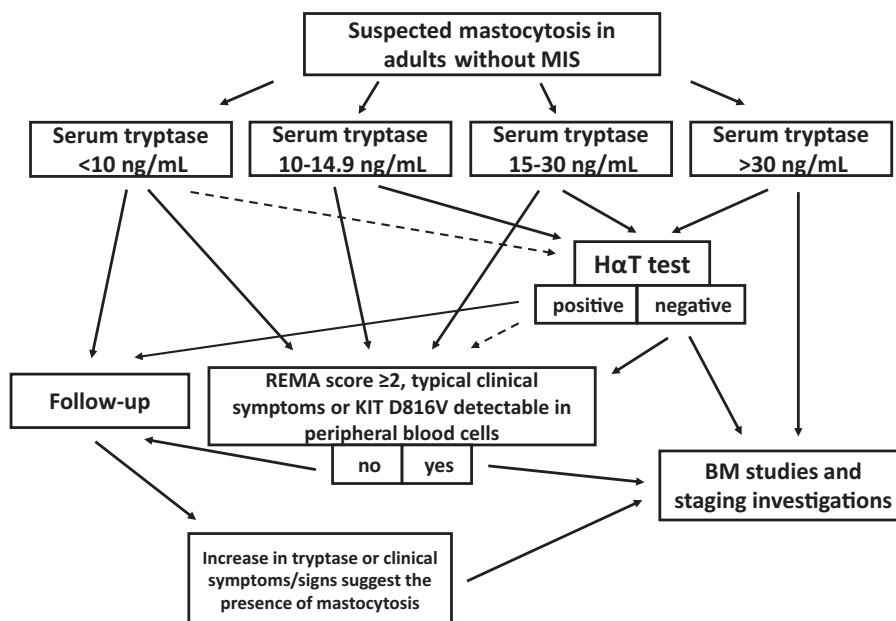
FIGURE 2. Diagnostic algorithm for patients with suspected SM without skin lesions when the test for HαT is available. Most carriers of HαT present with an elevated serum basal tryptase. When tryptase level is more than 30 ng/mL and the HαT test result is negative, the likelihood that the patient has SM or another myeloid neoplasm is high and a BM examination is highly recommended. When the tryptase level is less than 30 ng/mL, the REMA score should be applied and blood leukocytes examined for *KIT* p.D816V. In those with *KIT* p.D816V+ leukocytes and/or a "high-risk" REMA score, a BM examination is recommended. When the serum tryptase level is either normal or only slightly elevated, the patient may be followed without a BM examination. In this setting, a positive HαT test result is helpful because it decreases the likelihood of an undetected myeloid neoplasm. *MIS*, Mastocytosis in the skin; *REMA*, Red Española de Mastocitosis.

comparison between the baseline and event-related serum tryptase level (Figure E1).[44,45] When the event-related tryptase level exceeds 120% of baseline + 2 ng/mL, the likelihood is high that the patient is suffering from MCAS.[12,13]

A frequently asked question is whether patients with MCAS and/or HαT should undergo a BM examination.[44] We are of the opinion that patients with MCAS or HαT should have a BM examination only when they exhibit clear signs of SM, such as typical skin lesions, a KIT-activating mutation, an unexpectedly high tryptase level (eg, much higher than expected from the HαT test), steadily increasing tryptase levels, splenomegaly, unexplained osteoporosis, bee or wasp venom-induced or spontaneous anaphylaxis, a REMA score of 2 or more, and/or blood cell count abnormalities.[44,45]

DIAGNOSTIC ALGORITHMS AND CLASSIFICATION OF SM

Once the diagnosis of SM has been established, the subtype of SM should be defined by WHO criteria.[7,13-16,46] These criteria provide 6 SM variants: BM mastocytosis (BMM), indolent SM (ISM), smoldering SM (SSM), SM with an associated hematologic neoplasm (SM-AHN), aggressive SM (ASM), and MC leukemia (MCL).[7,15,16,46,47] The initial 3 categories are collectively called "nonadvanced SM," and the latter are referred to as "advanced SM" (Table E1). The prognosis of patients with nonadvanced SM is better than that of patients with advanced SM.[15-17,27-29,48]

In each variant of SM, patients can be further separated into subvariants, on the basis of clinical and laboratory findings. For

example, patients with ISM can be divided into patients with ISM with skin lesions and patients with ISM without skin lesions.[47] Cases with ISM without skin lesions have to be distinctively differentiated from patients with BMM and those with advanced SM on the basis of recently defined criteria.[46,47] This is of particular importance because in patients with advanced SM, skin lesions are often absent and the prognosis is less favorable compared with BMM or ISM (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).[47,48]

In patients with SM-AHN, the exact type of SM and of the associated hematologic neoplasm (AHN) variant should be defined and included in the final report.[7,10,13-16,46] Patients with ASM should be separated into those with ASM without transformation (MCs <5% in BM smears) and those with ASM in transformation to MCL (MCs in BM smears 5%-19%).[14,46] Patients with MCL may be divided into patients with primary (*de novo*) and secondary MCL (arising from another SM variant or MCS), acute MCL (with SM-induced organ damage = C-Findings) and chronic MCL (without C-Findings), MCL with or without an AHN, and leukemic MCL (circulating MCs ≥10% of leukocytes) and aleukemic MCL (<10% circulating MCs) (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).[14,46]

Finally, in all variants and subvariants of SM, patients can be divided into those with severe mediator-related symptoms (requiring anti−mediator-type drugs) and those with mild or no symptoms. In those with severe symptoms requiring therapy, the final diagnosis of SM should be labeled with the appendix SY (Figure 4).[7,10,13] For example, symptomatic cases with ISM are then designated as having ISM_{SY}. In patients with SM_{SY},

TABLE I. Clinical and laboratory findings indicative of SM in adults and major differential diagnoses (DD) that have to be considered

Feature/finding	Estimated frequency in SM	Specificity	Major DD
Typical skin lesions	>80%	++	CM in adults
Splenomegaly	10%	−	Other hematologic diseases and various internal disorders and infectious diseases
Hypotension/syncope	20%	+/−	Cardiac disorders, other internal disorders, infection, dehydration
Unexplained anaphylaxis	5%-10%	+/−	Allergy, intolerance
Anaphylaxis in the context of a hymenoptera venom allergy	10%	++	Venom allergy
Osteopenia/osteoporosis (otherwise unexplained)	20%	+/−	Other internal disorders
Osteosclerosis	30%	−/+	Other myeloid disorders
Cytopenia	10%	−	Hematologic disease
Leukocytosis	<10%	−	Hematologic disease
Thrombocytosis	<10%	−	Hematologic disease
Circulating MCs	<10%	++	MML, basophilia
Eosinophilia	10%-20%	−	Hematologic disease
Basal tryptase >15-30 ng/mL	20%-40%	+/−	CM, HαT, other myeloid neoplasms
Basal tryptase >30 ng/mL	>50%	+	HαT, other myeloid neoplasms
Basal tryptase >100 ng/mL	10%	++	Other myeloid neoplasms, HαT*
Elevated alkaline phosphatase	<10%	−/+	Liver or bone disease
KIT p.D816V in PB leukocytes	80%-90%	++	(other KIT D816V+ myeloid neoplasms)†

MML, Myelomastocytic leukemia; *PB*, peripheral blood.

*In carriers of HαT with multiple copy numbers of the *TPSAB1* gene, serum tryptase levels may exceed 100 ng/mL.

†In acute myeloid leukemia, *KIT* p.D816V may be detected in the absence of SM.

mediator-related symptoms may be severe or even life-threatening, and in those with anaphylaxis, MCAS may be diagnosed (Figures 3 and 4 and Figure E1).

HEMATOLOGIC PROGNOSTICATION IN PATIENTS WITH SM

A first important step in the prognostication of patients with SM is to apply the diagnostic WHO criteria and to define the correct disease variant.[7,9-11,13-16,46] It is critical to confirm that the patient indeed has SM but not pure CM, because the prognosis of CM is better than that of SM, including patients with ISM.[24,35,47] It is equally important to differentiate between BMM (very good prognosis), ISM (good prognosis), and SSM (good prognosis in most patients), and also between BMM and advanced SM without skin lesion (poor prognosis).[24,35,47] There are also major differences regarding prognosis and outcomes when comparing variants of advanced SM. In particular, patients with ASM in transformation or MCL have a worse prognosis compared with patients with ASM without signs of transformation.[14,48,49] In those with SM-AHN, the prognosis is usually dictated by the type of AHN (eg, ISM with an acute leukemia) but may also be dictated by the type of SM (eg, ASM or MCL with concomitant low-risk myelodysplastic syndrome).

Once the variant of SM has been defined, (1) additional prognostic variables are examined and (2) prognostic scores are applied. Individual variables that are relevant concerning progression include age, number and severity of cytopenia(s), basal serum tryptase level, *KIT* D816V allele frequency in blood leukocytes, alkaline phosphatase, beta-2 microglobulin, plasma IL-6 levels, cytogenetic lesions, molecular abnormalities (eg, *SRSF2*, *ASXL1*, or *RUNX1* mutations), and organomegaly.[15-23,50-52] In

addition, a rapid progression is indicative of a poor prognosis in advanced SM.[53]

Once individual prognostic factors have been identified, scoring systems should be applied. For patients with non-advanced SM, we recommend the International Prognostic Score for Mastocytosis (IPSM) and the Global Prognostic Score for SM optimized for Progression-Free Survival (GPSM-PFS).[27,29] For patients with advanced SM, we recommend the IPSM, the GPSM optimized for Overall Survival (GPSM-OS), and the molecular-adjusted score for mastocytosis (Mutation-Adjusted Risk Score [MARS]).[27-29] A user's guide and compass for application of prognostic scoring systems together with score variables are shown in Figure 5. The advantage of the IPSM and GPSM-PFS (over GPSM-OS and MARS) is that they are based on simple parameters and therefore ready to use in all centers and all patients.[27] However, unlike GPSM-OS and MARS, the IPSM and GPSM-PFS do not include molecular parameters. Therefore, we recommend applying these scores in a step-wise fashion on the basis of availability of molecular test results. In such an algorithm, the IPSM (or GPSM-PFS) would be applied first, and once all data from molecular analyses are available, the MARS and/or GPSM may then be applied. An advantage of the GPSM is that it is split into 2 subscores, a GPSM adjusted for optimal prediction of overall survival (GPSM-OS) and one optimized for predicting progression-free survival (GPSM-PFS) (Figure 5, B).[29]

On the basis of scoring results, patients can then be divided into low- or high-risk patients regarding progression and survival, which greatly assists in preparing an individualized management plan.[27-29] For example, in high-risk patients with SSM, shorter time intervals to control the course of disease are required and once the disease progresses, early treatment with KIT-targeting drugs may avoid rapid progression to MCL.
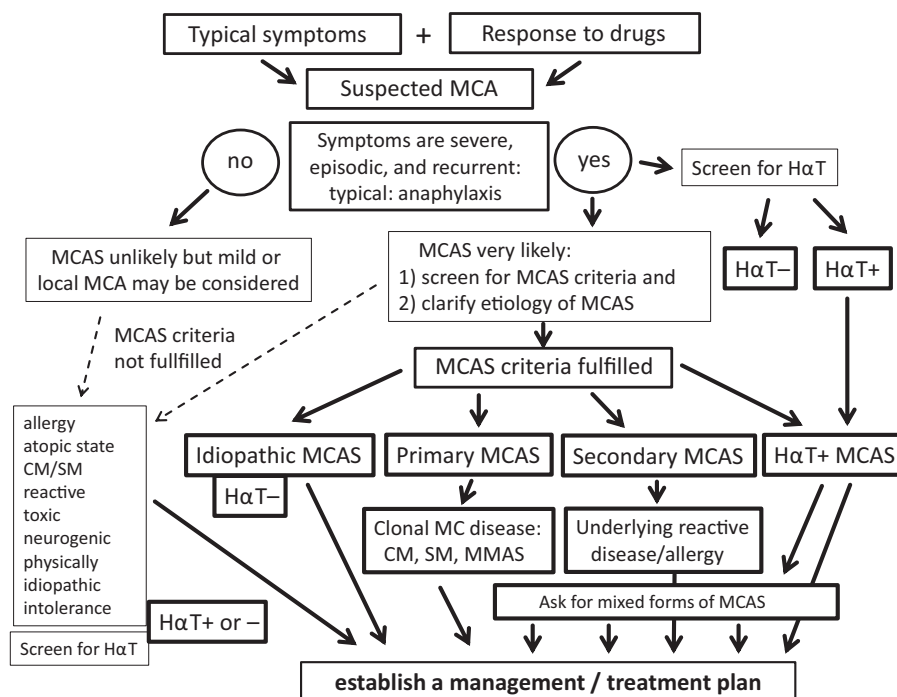
FIGURE 3. Proposed algorithm for patients with suspected MCAS. When the symptoms are typical (severe and episodic), the likelihood of MCAS is high and consensus criteria are applied to confirm MC involvement. Next, the underlying etiology is explored. In some cases, more than 1 underlying disease may be present (eg, mastocytosis and allergy). When available, the physician will also perform a PCR test for HαT. MCAS is classified into primary (clonal) MCAS, secondary MCAS (usually with an IgE-dependent allergy), idiopathic MCAS, and MCAS associated with HαT. For mastocytosis, typical indicators are a persistently elevated serum tryptase level and detection of KIT p.D816V. In many patients, a combined (mixed) form of MCAS is diagnosed. HαT per se is not considered to induce severe symptoms of anaphylaxis but is often detected in patients with combined (mixed) MCAS. In a final step, the management plan is established. *MCA*, Mast cell activation; *MMAS*, monoclonal MCAS.

TABLE II. Typical clinical findings and symptoms in patients with MCAS

Acute episodic symptom	Typical for MCAS
Anaphylaxis	++
Anaphylactic shock	++
Hypotension and tachycardia	+/−
Flushing	++
Pruritus	+
Urticaria	++
Angioedema	+
Wheezing	+/−
Throat swelling	+/−
Hoarseness	+/−
Headache	+/−
Diarrhea	+/−
Neuropsychiatric symptoms	+/−

To count as a sign (criterion) of MCAS, these symptoms need to be episodic, severe, and recurrent, and cannot be explained by any other known disorders or condition. ++, higher specificity; +, moderate specificity; +/−, low specificity.

It is worth noting that patients with SM-AHN should also undergo prognostication regarding their AHN. For example, in patients with SM and concomitant acute myeloid leukemia (AML), the WHO-defined type of AML and related prognostic variables, including karyotype and next-generation sequencing profiles, should be determined.[10,14,15] In this regard, it is important to know that in the context of SM, AML should be considered as high-risk (secondary) AML, which is important when establishing a management plan.[55-57]

Another important point is that ASM or MCL may sometimes evolve from an MCS. In these patients, the disease often progresses rapidly and the prognosis is dismal regardless of the presence or absence of risk factors or scoring results.[55-57] It is also worth noting that in patients with true MCS (no systemic involvement), no mutations in *KIT* and no mutations in other classical driver genes (*SRSF2*, *ASXL1*, *RUNX1*) are detectable. The prognosis is extremely poor in these patients.[58-60] Therefore, patients with MCS should always be managed in the same way as patients with high-risk ASM or acute MCL, in addition to excision and/or local radiation therapy where applicable.

DIAGNOSIS AND CLASSIFICATION OF MCAS: DELINEATION OF UNDERLYING COMORBIDITIES, THE GENETIC RISK, AND CLINICALLY RELEVANT TRIGGERS IN SM

The diagnosis of MCAS is based on diagnostic criteria presented in Table E4 in this article's Online Repository at www. jaci-inpractice.org and include (1) typical clinical symptoms (multiorgan, episodic, systemic, usually anaphylaxis), (2) an

FIGURE 4. User's guide for estimating the risk of severe mediator-related symptoms and anaphylaxis in patients with SM and for establishing individualized therapy. Patients with SM are divided into those with mediator-related symptoms requiring continuous therapy (SM$_{SY}$) and those who do not require such therapy. In most patients without symptoms, only prophylactic therapy is considered. In those with overt MCAS, the type of MCAS is defined and a test for HαT is performed when available. On the basis of type of MCAS and the presence of HαT, patients with SM are then classified according to the risk of anaphylaxis (MCAS). High-risk patients often have a mixed form of MCAS. For example, these patients have SM, are HαT carriers, and have an IgE-dependent allergy. For all patients, a detailed management plan has to be established.

event-related increase in the basal serum tryptase level to more than 120% of baseline plus 2 ng/mL (or a diagnostic increase [100% over baseline] in 24-hour urine N-methyl histamine and/ or 2,3-dinor-11β-PGF$_{2α}$, and leukotriene E$_4$ if tryptase is not available), and (3) the response of the symptoms to drugs targeting MC mediators, mediator effects, or MC activation (Table E4).[12,13,44] Diagnostic MCAS criteria apply to patients with SM in the same way as in patients without SM, regardless of the underlying pathology, basal tryptase, type of allergen, or HαT status.

A number of genetic patterns and comorbidities are considered to contribute to the manifestations and severity of MC activation and MCAS in patients with SM. One well-documented genetic variable appears to be HαT.[40,41] This genetic trait is characterized by an increase in the alpha tryptase gene (TPSAB1) copy number and elevated serum tryptase levels.[61,62] HαT carriers are more frequently detected among patients with SM compared with healthy controls and are also more frequently detected in patients with nonadvanced SM compared with those with advanced SM.[40,41,63] Most significantly, however, the prevalence of severe mediator-related symptoms and thus MCAS in SM is higher in carriers of HαT compared with patients with SM without HαT.[40,41] In fact, recurrent anaphylaxis is often detected in HαT+ patients with SM, especially when an IgE-dependent allergy is also present. These patients are at high risk for the development of life-threatening anaphylaxis (Figure 4). In about half the patients, an underlying IgE-dependent trigger (allergen) can be identified, whereas in the remaining cases, it is difficult or impossible to define the event-inducing agent. It is also important to know that baseline tryptase levels may vary in patients with HαT.

Therefore, alternative methods to determine changes in tryptase levels over baseline have recently been proposed for such cases.[64]

Based on definitions provided by the consensus group, MCAS is divided into primary MCAS where clonal MCs are detected (most patients have SM), secondary MCAS where MCs are nonclonal (and usually an IgE-dependent allergy is detected), and idiopathic MCAS where neither clonal MCs nor an underlying allergy or other reactive disease process causing MC activation can be identified (see Table E5 in this article's Online Repository at www.jaci-inpractice. org). On the basis of this classification, all patients with SM are diagnosed as having primary (monoclonal) MCAS when MCAS criteria are met. As mentioned before, in a subset of these patients, an underlying allergy (and/or HαT) is also detected. Therefore, these patients are often regarded as suffering from a mixed (combined) form of MCAS, which is of clinical significance because of the particularly high risk to develop life-threatening anaphylaxis, especially when HαT is also present (Figure 4). Such patients require special attention and medical care (Figure 4).[44-46]

There is also a debate about the diagnostic impact of HαT in the context of MCAS. Because HαT is a hereditary condition but not a disease per se, one consideration for discussion is to change the diagnosis from idiopathic MCAS to HαT+ MCAS when MCAS criteria are fulfilled in an HαT carrier (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). When several family members fulfill MCAS criteria, the term hereditary (familial) MCAS may be appropriate. Most of these patients will be diagnosed with a mixed form of MCAS.

Finally, it should also be noted that not all patients who may have some degree of reactions produced by MCs fall within the definition of MCAS applied in this work, and in these cases, other diagnoses have to be considered.

FIGURE 5. Structured approach for hematologic prognostication of patients with SM. (**A**) First, the diagnosis of SM and the type of SM are established using WHO criteria. Overall, patients are classified as having nonadvanced or advanced SM. Nonadvanced SM includes BMM, ISM, and SSM. Advanced forms include ASM, SM with an associated hematologic (non-MC) neoplasm (SM-AHN), and MCL. Three validated scoring systems are depicted: the IPSM, the GPSM, and the MARS. These scores are applied step-wise on the basis of available data and type of SM: in a first step, the IPSM or GPSM-PFS can be applied to all patients, including those with nonadvanced and advanced SM. When all molecular test results are available, the GPSM-OS and MARS are then applied to patients with advanced SM. (**B**) Score points and score-based risk categories established with the individual scores. Other scores may also be considered: the Mutation-Augmented Prognostic Scoring System for advanced SM[54] and the Clinical Risk Score.[28] *AdvSM*, Advanced SM; *AP*, alkaline phosphatase; *ß2MG*, beta-2 microglobulin; *Hb*; hemoglobin; *Int*, intermediate; *NGS*, next-generation sequencing; *PLT*, platelet count; *U/L*, units per liter; *WBC*, white blood count.

GENERAL MANAGEMENT PLAN FOR PATIENTS WITH NONADVANCED SM

Patients with BMM, ISM, and SSM should be examined for the presence, type, and severity of mediator-related symptoms, specific organ involvement, and certain comorbidities at first presentation and during follow-up.[10,13] In addition, all relevant laboratory parameters, including the basal serum tryptase level, blood cell counts, and serum chemistry as well as all relevant staging investigations, including an ultrasound and/or computed tomography of liver, spleen, and lymph nodes, osteodensitometry, gastrointestinal endoscopy (depending on symptoms), and allergy diagnostics (as needed), should be performed at first presentation and as appropriate in follow-up visits.[10,13]

The time interval for follow-up visits depends on the type of SM, clinical course, and overall risk profiles. For example, in patients with stable BMM or ISM without any signs of osteopathy or other organ dysfunction, yearly office evaluation will usually be sufficient. In contrast, in patients with SSM and signs of disease progression, or patients with ISM and severe osteoporosis, shorter time intervals are required.

TABLE III. Step-wise approach to treat mediator-induced symptoms related to MCA in patients with SM

Drug or preventive measure	Indication(s)
Basic management:	
1. Avoidance of any triggers	Prophylaxis against anaphylaxis
2. Basic therapy with HR1 blocker plus HR2 blocker	Prophylaxis against anaphylaxis, mediator-related symptoms
Additional therapies and measures:	
3. Adding a proton pump inhibitor to the HR2 blocker	Gastrointestinal symptoms not controlled by HR2 blocker
4. Adding cromolyn sodium	Refractory skin or gastrointestinal symptoms
5. Adding ketotifen, aspirin, or a leukotriene receptor antagonist (eg, montelukast)	Refractory flushing, tachycardia, hypotension, or bone pain*
6. Adding ultraviolet light therapy†	Refractory skin symptoms
7. Adding corticosteroids	Refractory allergic symptoms, anaphylaxis, MCAS
Additional specific therapies:	
8. Insect venom immunotherapy	Bee or wasp venom allergy
9. Omalizumab therapy	Multiresistant allergic symptoms, therapy-refractory MCAS, confirmed IgE-dependent allergy in high-risk patients (prophylaxis)
10. Adrenaline and other emergency drugs used in anaphylaxis	Anaphylactic shock (MCAS event)
11. Midostaurin or avapritinib	MCAS in patients with advanced SM (reducing target cells and releasability)

HR, Histamine receptor; LTE_4, leukotriene E_4; *MCA*, MC activation; PGF_2, prostaglandin F_2.

*The recommendation to use aspirin or a leukotriene receptor antagonist in patients with mastocytosis is often based on and supported by the demonstration of an increase in the urinary prostaglandin D_2 metabolite 2,3-dinor-11β-$PGF_{2\alpha}$ and LTE_4.

†Because of the risk of secondary skin cancer, this therapy is no longer recommended for the treatment of cutaneous lesions in mastocytosis in most centers.

In all patients with SM, individual risk factors and scoring systems should be applied to estimate the overall prognosis and the risk of hematologic progression.[27-29] In the follow-up, relevant "noninvasive" prognostication markers include blood cell counts, the basal serum tryptase level, alkaline phosphatase, beta-2-microglobulin, and the *KIT* p.D816V allele burden in blood leukocytes.[17-20,31,46,53,65,66] When 1 or more of these parameters increase substantially in repeated determinations, reexamination of the BM and of all relevant disease parameters is recommended.[13,17-20,46,66] Next-generation sequencing (myeloid panel) is also performed in these patients.[17-20,31,54] BM examinations at diagnosis and in the follow-up (suspected progression) include a detailed histomorphologic and immunohistochemical evaluation of BM cells, conventional cytogenetic studies and fluorescence *in situ* hybridization, flow cytometry studies, and molecular studies, including next-generation sequencing.[10,13,17-20]

TREATMENT OF MEDIATOR-RELATED SYMPTOMS: BASIC THERAPY FOR PATIENTS WITH SM

The most important therapeutic maneuver in symptomatic patients is to avoid any relevant triggering factors or conditions that may provoke a reaction.[8-11] Medical personnel need to assist patients in learning how to avoid those factors and situations that trigger adverse events. An allergy evaluation and appropriate testing may be helpful, keeping in mind the possibility of false-negative test results.

The basic therapy for all patients with SM consists of a combination of histamine receptor (HR)1 and HR2-blocking drugs.[7-11,30-32] In asymptomatic patients, the prophylactic administration of these drugs is often recommended.[8-12] In addition to antihistamines, mediator-related symptoms may be treated with MC-stabilizing agents or other targeted drugs, such as cromolyn sodium or ketotifen where available.[67-69] In other patients, prostaglandin D_2 or leukotrienes may play a role as key mediators, and in these cases, drugs targeting arachidonic acid production or leukotriene receptors (eg, montelukast) may be considered.[69-71] In resistant cases, corticosteroids are often recommended. In most patients, the symptoms that derive from MC activation can be managed with these agents. If this is not the case, more specific treatments should be considered. These include specific immunotherapies (especially in patients with bee or wasp venom allergy) and/or an anti-IgE antibody, such as omalizumab.[72-79] In patients with SM suffering from bee or wasp venom allergy, life-long immunotherapy is recommended.[31,33,74,80] In severe, treatment-resistant cases, combinations of the aforementioned drugs and approaches may be required.[81-84] In these patients, a high burden of MCs may sometimes be documented. For these cases, additional treatment with drugs capable of reducing MC numbers may be considered to bring anaphylaxis under control. Such drugs, including cladribine (2CdA), midostaurin, and avapritinib, are usually considered only for patients with advanced SM.[85-91]

Avapritinib may be especially effective in eradicating most or all neoplastic (*KIT* p.D816V+) MCs. Midostaurin, in turn, has the capacity to inhibit IgE-dependent mediator release from MCs.[92,93] In patients with nonadvanced SM, such therapy should be undertaken only after careful consideration and possible consultation with physicians at a center of excellence (of ECNM or AIM) and preferentially within clinical studies where available.[94] Table III provides a summary of treatment options for patients with SM suffering from mediator-related symptoms.

MANAGEMENT OF MCAS IN SM: SELECTION OF TARGETED DRUG THERAPIES AND DEVELOPMENT OF PERSONALIZED TREATMENT APPROACHES

The management of MCAS in patients with SM is a clinical challenge, especially when symptoms are severe and resistant against conventional anti–mediator-type drugs.[12,13,45] In some

of these patients, a combined form of MCAS (primary and secondary with or without HαT) is diagnosed. However, not all patients with SM and MCAS are HαT carriers, and in some of these cases, no IgE-dependent allergy is detected. In other patients, IgE-dependent allergies are detected only after treatment-induced reduction of the MC burden.

Table III presents a summary of treatment options for patients with MCAS, including prophylactic approaches and emergency treatment. All patients at risk for anaphylaxis are advised to routinely take all prescribed medications, to avoid known triggers, to inform all doctors and caregivers about their disease, to be taught the importance of supine positioning to counter hypo-perfusion from hypotension, and to carry 2 to 3 adrenaline self-injectors, after having been instructed about application and potential consequences and having an action plan in place.

Treatment of systemic reactions in patients with MCAS who also have SM follows the general recommendations for the treatment of anaphylaxis, with recognition that drugs targeting MC activation and/or MC-mediator effects are essential.[82-84] A management plan including prophylactic therapy should be established and maintained during symptom-free intervals. In resistant cases, one strategy is to increase the dose of HR1 and HR2 blockers and to consider corticosteroid therapy. However, long-term treatment with corticosteroids should be avoided if possible. In those with a known IgE-dependent allergy against insect venom, life-long immunotherapy is recommended.[72-74] Another strategy for such patients is to consider omalizumab therapy as additional prophylaxis.[75-79] Finally, in patients with a very high MC burden (advanced SM), therapy with cytoreductive agents including 2CdA or novel KIT D816V-targeting drugs such as midostaurin or avapritinib can reduce MC numbers and may thereby help avoid more serious MCAS events.[86-89,94] Avapritinib may be the most potent drug regarding suppression of MC development in patients with advanced SM, whereas midostaurin is known to exhibit additional inhibitory effects on IgE-dependent MC activation.[92,93] At the writing of this article, both midostaurin and avapritinib have been approved only (in the United States) for use in patients with advanced SM, and no long-term studies in patients with MCAS (to show efficacy in prevention of MCAS events) or those with nonadvanced SM are available.

MANAGEMENT OF OSTEOPATHY IN PATIENTS WITH SM

Osteopenia and osteoporosis are major complications reported in all forms of SM.[95-101] Both female and male patients may be affected, and the risk for vertebral fractures is rather high, especially when progressive osteopathy is documented. An essential approach is to ask for height- and weight-changes in the follow-up and to perform osteodensitometry (T-score) evaluations at regular time intervals to estimate the fracture risk.[10,100] In addition, vitamin D levels should be examined during follow-up.

All patients are advised to avoid physical inactivity, obesity, and long-term treatment with corticosteroids (see Table E6 in this article's Online Repository at www.jaci-inpractice.org). Furthermore, all patients who suffer from vitamin D deficiency should receive appropriate vitamin D supplementation together with vitamin K2. In those who suffer from a substantial osteopenia (T score <-2) or overt osteoporosis (T score <-2.5), treatment with a bisphosphonate or a receptor activator of nuclear factor kappa beta inhibitor is generally recommended (see

Figure E3 and Table E6 in this article's Online Repository at www.jaci-inpractice.org).[10,102-105] If these therapies fail, low-dose IFN-α may be considered.[101,103]

In a few patients with advanced SM, areas of larger osteolyses (up to several centimeter in diameter) may also be detected. In these patients, specific therapy (KIT-targeting drugs, cladribine, or chemotherapy) should be initiated and a bisphosphonate and/or a receptor activator of nuclear factor kappa beta inhibitor considered as an addition. Radiation may also be considered for pain relief but is not considered standard therapy of osteolysis in the context of SM. Table E6 presents a summary of risk factors for osteoporosis in SM and management recommendations provided by our consensus group.

MANAGEMENT OF ADVANCED SM AND HEMATOLOGIC PROGRESSION: PROPOSED STRATEGIES AND THERAPEUTIC ALGORITHMS

Treatment of advanced SM remains a clinical challenge for several reasons, the most important being that advanced SM exhibits a complex pathology, with variable clinical presentations and unpredictable courses.[7-11,14-17,46-48] Important initial questions are whether and/or what form of AHN is present, whether most clonal cells exhibit KIT p.D816V (or other KIT mutant forms), and whether the disease is slowly or rapidly progressing.[7,10,14-17,48,50] Additional important questions are whether the patient is in a high-risk category by a scoring analysis (IPSM, GPSM, MARS)[27-29] (Figure 5), would qualify as a transplantation candidate, and would have a suitable stem cell transplant donor.[14-17,48,53,106] Finally, the presence and extent of organ damage has to be integrated into the management plan.

For patients with KIT p.D816V+ ASM or MCL (most or all neoplastic cells display KIT p.D816V) with slow progression, the KIT D816V-targeting drugs midostaurin and avapritinib are regarded as first-line therapy.[17,87-91] Because of a reported risk of intracranial hemorrhage, use of avapritinib is generally restricted to patients with a platelet count above 50,000/μL of blood unless the dose of avapritinib is reduced to where it is not believed to be associated with an increased risk of intracranial hemorrhage. For rapidly progressing patients with KIT p.D816V+ ASM or MCL, avapritinib may be regarded as a preferred drug and considered as first-line therapy when the drug is available.[17] If this is not the case, polychemotherapy regimens including midostaurin or cladribine should be contemplated, especially in patients with rapidly progressing MCL. When these patients are young and eligible and achieve a good response or even hematologic remission, subsequent consolidation with hematopoietic stem cell transplantation should be considered.[106-108] The same holds true for patients with MCS progressing to MCL.[109] Figure E2 shows a proposed treatment algorithm for patients with advanced SM.

In a small subset of patients with advanced SM, neoplastic cells express wild-type KIT or rare juxtamembrane KIT mutations. In these patients, some of which have SM with a well-differentiated MC morphologic, imatinib may be effective in reducing MC numbers and may sometimes even induce a complete remission.[110-112]

In patients with SM-AHN, the clinical course is often dictated by the AHN, and sometimes by both the (advanced) SM and the AHN. Therefore, it is crucial to define the exact nature (subtype) and final diagnosis for both the SM and AHN components using

WHO criteria.[7,10,14-17,48,53] In addition, it is important to know whether AHN cells exhibit *KIT* p.D816V. For example, in most patients with SM-CMML and about half the patients with SM-AML, AHN cells express *KIT* p.D816V,[55-57] which may lead to the conclusion that the patient should receive midostaurin or avapritinib. In general, management and treatment of the AHN should be planned as if no SM was diagnosed with recognition that AML counts as high-risk (secondary) AML in the context of SM. In addition, the SM portion of the disease should be managed as if no AHN was diagnosed. For eligible patients who respond to polychemotherapy or targeted drugs, allogeneic hematopoietic stem cell transplantation should be considered.[106-108] When AML blasts display *KIT* p.D816V and/or ASM-AML is diagnosed, a potential strategy is to combine polychemotherapy with midostaurin in the same way as in *FLT3*-ITD—mutated AML. An alternative may be to combine avapritinib with anti-AML drugs as an experimental approach, provided that platelets remain above 50,000/μL of blood.

SUMMARY AND FUTURE PERSPECTIVES

Mastocytosis is a multifaceted neoplasm with various manifestations and complications, and a heterogeneous clinical course that requires a multidisciplinary approach and patient-specific, personalized management. Patients with SM variably suffer from skin lesions and cosmetic problems, mediator-related symptoms, IgE-dependent allergies, gastrointestinal problems, and/or cardiovascular symptoms. A serious complication is anaphylaxis, which may occur in the form of an overt MCAS. In addition, patients may suffer from severe osteoporosis and multiple bone fractures. Another serious complication is hematologic progression. Using currently available diagnostic criteria, SM can be diagnosed and classified in all patients. In addition, the degree of organ damage can be quantified. Moreover, various scoring systems are available through which the risk of hematologic progression can be determined. Finally, a number of genetic and patient-related risk factors for the occurrence of MCAS, osteopathy, or leukemia in SM have been identified. When taking all these factors, scores, and risk profiles into account, an optimal management plan can be established for each patient, following the principles of personalized medicine. In general, management plans are based on 5 main strategies: patient information, follow-up investigations, avoidance of risk factors, prophylactic therapies, and interventional therapies. Our proposed algorithms and recommendations should provide a standard guide and compass for diagnostic approaches, prognostication, and management of patients with SM and/or MCAS. This guide should facilitate precise diagnosis and prognostication and optimal management of all patients in daily practice.

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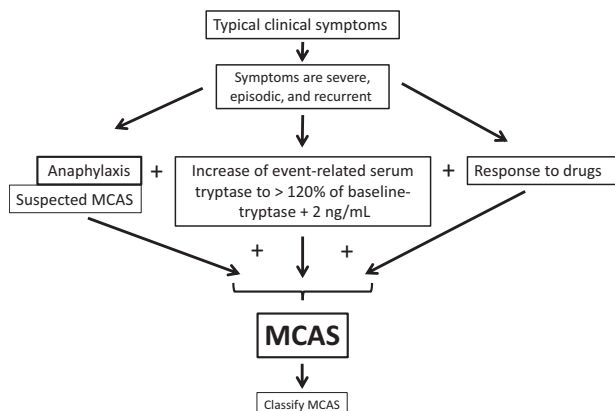
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FIGURE E1. Application of diagnostic criteria of MCAS. When clinical symptoms of MC activation (MCA) are detected, these symptoms are then divided into (1) local vs systemic, (2) acute and episodic vs chronic, (3) severe vs less severe (mild), and (4) recurrent vs nonrecurrent. When symptoms are systemic, episodic, severe, and recurrent, the physician will screen for definitive signs of an MCAS. The presence of anaphylaxis increases the likelihood that the patient is suffering from MCAS. The diagnosis is further supported by demonstration of an event-related increase in the serum tryptase to more than 120% of the individual's baseline $+$ 2 ng/mL, which supports the involvement of the MC lineage. When MCA-related symptoms also respond to drugs stabilizing MCs or blocking MC-mediator effects, the diagnosis MCAS can be established. Finally, MCAS is then classified into MCAS variants.
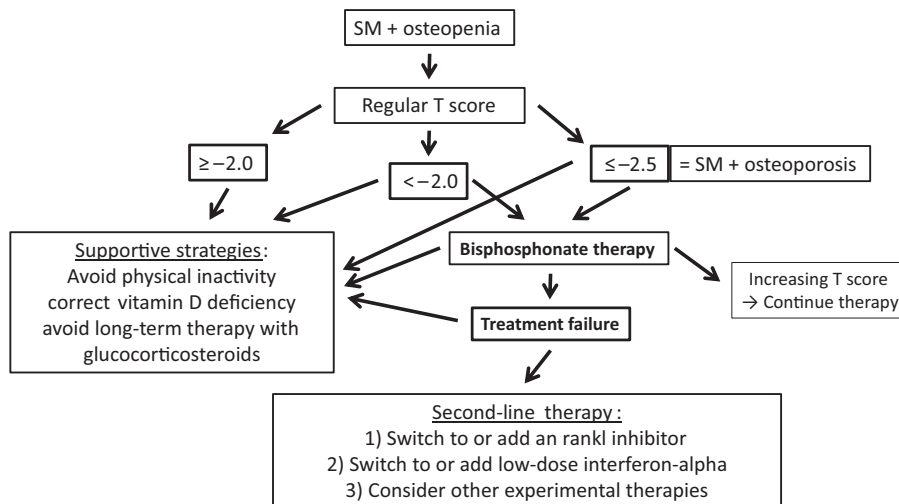
FIGURE E2. Management of patients with SM and osteopenia/osteoporosis. Osteodensitometry is an integral component of the initial staging in adult patients with SM. When the T score is −2 or higher, conventional preventive and supportive measures and treatments are recommended, including structured physical activity, weight loss (in case of obesity), vitamin D supplementation, and avoidance of long-term corticosteroid therapy. When the T score is below −2.0 (severe osteopenia) or below −2.5 (osteoporosis), a bisphosphonate therapy is usually recommended (after having excluded potential contraindications). When under such therapy, the T score improves (increases), treatment will be continued. In the case of treatment failure, second-line drugs should be considered, such as an RANKL inhibitor, low-dose IFN-α, or other experimental therapies. It should be emphasized that with all such treatments, definitive evidence for beneficial drug effects from larger controlled clinical trials is lacking. Therefore, all these treatments must be regarded as based on expert advice and expert experience. *RANKL*, Receptor activator of nuclear factor kappa beta.
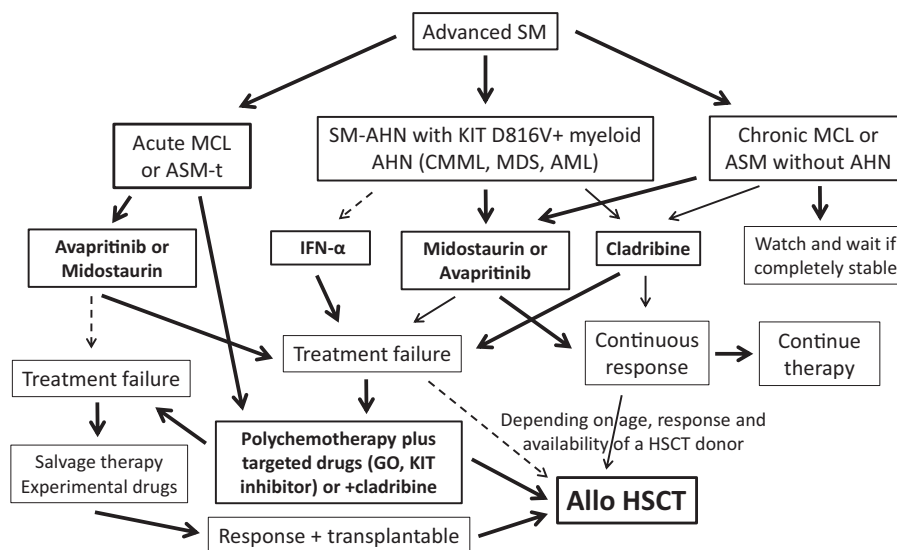
FIGURE E3. Management of patients with advanced SM. After having established the diagnosis "advanced SM," the WHO category is defined and the patient evaluated for clinical and laboratory signs of (rapid) progression. In addition, the disease is studied for the presence of molecular targets, including KIT D816V. Patients with acute MCL or rapidly progressing ASM (= ASM in transformation = ASM-t) are either treated with KIT D816V-targeting drugs (midostaurin or avapritinib), or are candidates for polychemotherapy (AML-like regimens, often with midostaurin or cladribine) and subsequent hematopoietic stem cell transplantation (HSCT). Avapritinib is currently restricted to patients with a platelet count of more than 50,000/μL of blood or is applied in dose-reduced form. In case of resistance or relapse after drug therapy, salvage therapy (experimental drugs, polychemotherapy) is usually applied, and the patient is prepared for HSCT whenever possible. In patients with KIT D816V+ ASM, slowly progressing MCL, or SM with an associated hematologic (myeloid) neoplasm, avapritinib is at present considered first-line therapy, provided that the platelet counts are reasonable. If this is not the case or avapritinib is not available, midostaurin or cladribine is usually recommended. IFN-α, a drug that has been administered in advanced SM in the past, is no longer regarded standard therapy, except for a few cases with isolated mild liver involvement in which a combination of IFN-α and corticosteroids can often keep the ASM process under control. In those in whom no *KIT* mutation at codon 816 is detected, imatinib may be considered, with good responses seen in some patients with ASM or MCL. When there is no satisfactory response to chemotherapy, KIT-targeting drugs, and/or cladribine, the patient should be considered for HSCT (younger and fit patients) or for palliative therapy (standard palliative drug: hydroxyurea). In a very few patients with completely stable disease (chronic stable MCL, ASM without any signs of progression, or AHN), a wait and watch strategy may be considered. However, regular short-term follow-up investigations are required because most of these patients progress with some time. *Allo HSCT*, Allogeneic HSCT; *AML*, acute myeloid leukemia; *CMML*, chronic myelomonocytic leukemia; *GO*, gemtuzumab ozogamicin; HSCT, hematopoietic stem cell transplantation; *MDS*, myelodysplastic syndrome.

TABLE E1. MC disorders—Overview

Diagnosis-variant	Typical features and findings: Diagnostic criteria
MC hyperplasia	Increased numbers of mature MCs, no evidence of MC clonality
Mastocytosis	Expansion and accumulation of clonal MCs Meets diagnostic WHO criteria for mastocytosis
CM	Typical skin lesions, Darier's sign, no evidence for marked (diagnostic) involvement of other organs
SM	Evidence for diagnostic systemic involvement of internal organs (SM criteria fulfilled); skin lesions may or may not be detected
Nonadvanced SM variants:	No evidence of SM-induced organ damage
BMM	SM limited to the BM, no B- or C-Finding
ISM	SM with multiorgan involvement and 0 or 1 B-Findings and no C-Finding*
SSM	SM with multiorgan involvement and 2 or 3 B-Findings and no C-Finding*
Advanced SM variants:	
Aggressive SM	SM with multiorgan involvement and SM-induced organ damage = 1 or more C-Findings; skin lesions may be absent
SM-AHN	SM criteria fulfilled and WHO-based criteria for an AHN also fulfilled
MCL	MCs in BM smears ≥20%, C-Findings are detected in most patients; skin lesions are often absent; in the classical variant, circulating MCs are ≥10%
MCS	Local sarcoma-like MC tumor; no evidence of SM; SM criteria not fulfilled
Myelomastocytic leukemia (MML)	Expansion and accumulation of clonal MCs, underlying advanced myeloid neoplasm, often a myeloid leukemia; SM criteria are not fulfilled MCs in BM smears ≥10% MCs are usually immature and metachromatic blast cells are also identified
MCAS	MCAS criteria are fulfilled: typical clinical symptoms (anaphylaxis); event-related increase in serum tryptase levels to at least 120% + 2 ng/mL; patients typically respond to mediator-targeting drugs, MC-stabilizing drugs, or drugs that are able to block MC-mediator effects
Primary (clonal) MCAS	Clonal (*KIT* p.D816V+) MCs detected
Secondary MCAS	Underlying reactive/allergic disease found; in most patients, an IgE-dependent allergy is detected
Combined (mixed) MCAS	Criteria for primary and secondary MCAS are fulfilled
HαT+ MCAS	HαT is diagnosed and MCAS criteria are fulfilled
Idiopathic MCAS	No evidence for SM, MC clonality, HαT, or an underlying allergic/atopic/reactive disease that could act as primary trigger of MCAS

*B-Findings are indicative of the smoldering state and relate to a huge increase in the MC burden and expansion of the KIT D816V+ process into multiple hematopoietic lineages; C-Findings are indicative of SM-induced organ damage. Two or more MC disorders (eg, ISM and MCAS) may be detected in the same patient.

TABLE E2. Classification of mastocytosis: Prevalence of skin lesions and specific risk of hematologic progression and anaphylaxis

Variant and subvariant	Skin lesions*	Risk of progression†	Risk of anaphylaxis‡
CM			
Maculopapular CM	+	Very low§	Intermediate
Diffuse CM	+	Very low	High
Mastocytoma of skin	+	Very low	Low
SM			
BMM	−	Very low	High
ISM with skin lesions	+	Low	Intermediate
ISM without skin involvement	−	Low	Intermediate
SSM	+	Intermediate	Intermediate
SM-AHN	+	High	Low
ASM	+/−	High	Low
MCL	−/+	High	Low
MCS	−	Very high	Low

*Skin lesions score: +, in >75% of all patients; +/−, in 50%-75%; −/+, in 10%-49%; −, not detected or detected in <10% of all patients.

†Progression into a higher-grade MC neoplasm or from SM into SM-AHN. In MCL, the risk of progression and disease deterioration is also high, but the diagnosis often remains MCL unless the patient also develops an AHN.

‡Estimates based on clinical experience.

§Although the risk of progression in CM is very low, a few patients may develop SM.

TABLE E3. Refined classification and criteria for advanced SM, including SM-AHN, ASM, and MCL

Category	Subvariant	Defining key features (criteria)
SM-AHN	According to SM variant:	
	BMM-AHN	WHO criteria (consensus criteria) for SM variants
	ISM-AHN	
	SSM-AHN*	
	ASM-AHN	
	MCL-AHN	
	According to the AHN:	
	SM with myeloid AHN (SM-CMML, SM-AML, ...)	WHO criteria for myeloid AHN
	SM with lymphoid AHN (SM-ALL, SM-MM, …)	WHO criteria for lymphoid AHN
ASM	According to a previous MC neoplasm:	
	Primary ASM	No previous SM known
	Secondary ASM	Previous BMM, ISM, SSM, …
	According to an AHN	
	ASM without AHN	
	ASM-AHN	WHO criteria for AHN
	According to signs of progression:	
	ASM	<5% MCs in BM smears
	ASM in transformation (= ASM-t)	5%-19% MCs in BM smears
MCL	According to a previous MC neoplasm	
	Primary MCL	No previous MC disease known
	Secondary MCL	Previous BMM, ISM, SSM, MCS, …
	According to an AHN	
	MCL without AHN	
	MCL-AHN	WHO criteria for AHN
	According to organ damage	
	Chronic MCL	No C-Finding(s)
	Acute MCL	One or more C-Finding(s)
	According to blood involvement	
	Aleukemic MCL	MCs <10% of blood leukocytes
	Leukemic MCL	MCs ≥10% of blood leukocytes

ALL, Acute lymphoblastic leukemia; *AML*, acute myeloid leukemia; *CMML*, chronic myelomonocytic leukemia; *MCs*, mast cells; *MM*, multiple myeloma.

*SSM-AHN is an extremely rare condition because signs of myeloproliferation and/or dysplasia will be regarded as evidence of a (myeloid) AHN in almost all cases. However, SSM may still be diagnosed in a patient with AHN, eg, when the AHN is a lymphoid neoplasm (eg, SSM-ALL).

TABLE E4. Minimal diagnostic criteria for MCASs as defined by the consensus group[*]

A. Typical clinical signs of severe, recurrent (episodic) systemic MC activation are present (often in form of anaphylaxis) (definition of systemic: involving at least 2 organ systems)

B. Involvement of MCs is documented by biochemical studies: preferred marker: increase in serum tryptase level from the individual's baseline to plus 20% (=120%) + 2 ng/mL[†]

C. Response of symptoms to therapy with MC-stabilizing agents, drugs directed against MC-mediator production, or drugs blocking mediator release or effects of MC-derived mediators[‡]

PGD2, Prostaglandin D2.

[*]The consensus criteria for MCAS were first published in Akin et al[E1] and Valent et al.[E2] All 3 MCAS criteria (A + B + C) must be fulfilled to call a condition MCAS.

[†]Other MC-derived markers of MC activation (histamine and histamine metabolites, PGD_2 metabolites, heparin) have also been proposed but are less specific compared with tryptase.

[‡]Example: histamine receptor blockers.

TABLE E5. Classification of MCASs

Variant of MCAS	Main diagnostic features
Primary MCAS (clonal MCAS)[*]	A KIT-activating *KIT* mutation is detected and MCs aberrantly display CD25 in most cases (a) with confirmed mastocytosis (CM or SM)[†] (b) with only 2 minor SM criteria[†]
Secondary MCAS	An IgE-mediated allergy, another hypersensitivity reaction, or another immunologic disease that can induce MCA and thus MCAS is diagnosed, but no neoplastic MC or *KIT* mutation is found[‡]
HαT+ MCAS (hereditary/familial MCAS)	Criteria to diagnose MCAS are met, no related allergy or underlying clonal MC disease is detected, and the HαT test result is positive[§]
Mixed forms of MCAS	Criteria to diagnose MCAS are fulfilled, and various combinations of the above-described etiologies are demonstrable
Idiopathic MCAS	Criteria to diagnose MCAS are met, but no related reactive disease, no IgE-dependent allergy, and no neoplastic/clonal MCs are found[‡]

MCA, MC activation.

[*]The terms clonal MCAS and monoclonal MCAS (MMAS) can be used synonymously with the term primary MCAS. The most prevalent mutation in *KIT* found in these patients is D816V.

[†]Most of the patients suffer from CM or SM. However, in some cases, only 2 minor SM criteria are detected and criteria for SM and CM are not fulfilled.

[‡]No KIT-activating *KIT* mutations are detected, and flow cytometry (if performed) will usually not detect a clonal population of CD25-positive MCs.

[§]In HαT carriers without an allergy and/or SM, the incidence of anaphylaxis and thus MCAS is very low. Therefore, most of these patients have a mixed form of MCAS: in fact, these patients suffer from a concomitant allergy and/or SM. Whether a pure form of HαT+ (hereditary) MCAS exists is currently under debate. Currently, we prefer the descriptive term HαT+ MCAS. A diagnosis of hereditary (familial) MCAS would require an association between MCAS and HαT in multiple family members.

TABLE E6. Risk factors for osteoporosis in patients with SM

Risk factor	Specific measures and therapies
Obesity Physical inactivity	Weight control (diet) Physical exercise
Corticosteroid therapy	Avoidance of long-term treatment with corticosteroids (offer alternative drugs)
Vitamin D deficiency	Vitamin D supplementation (+ vitamin K2)[*]
Osteopenia	As soon as the T score drops to <−2, therapy with a bisphosphonate is initiated[†]
Heparin together with MC proteases	Avoid long-term heparin therapy, administer MC-stabilizing agents

[*]In a subset of patients, higher doses of vitamin D are required for supplementation. In these patients, vitamin K2 is added to avoid any risk of Ca-flux into the arterial vessels and thus the risk of atherosclerosis.

[†]Bisphosphonates are still considered first-line therapy in patients with high-risk osteopenia (T score <−2). It is important that all other measures and treatments to prevent progression of osteopenia into osteoporosis (right column) must also be maintained.

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