

## Review Article

# Mastocytosis: a paradigmatic example of a rare disease with complex biology and pathology

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**Abstract:** Mastocytosis is a rare disease characterized by abnormal expansion and accumulation of tissue mast cells (MC) in one or multiple organs. In most adult patients, systemic mastocytosis (SM) is diagnosed. Based on histopathological findings and organ damage, SM is divided into indolent SM (ISM), smoldering SM (SSM), SM with an associated hematologic non-MC-lineage disease (SM-AHNMD), aggressive SM (ASM), and MC leukemia (MCL). The clinical course and prognosis vary greatly among these groups of patients. In all variants of SM and most patients, neoplastic cells display the *KIT* mutation D816V. This suggests that additional *KIT*-independent molecular defects cause progression. Indeed, additional oncogenic lesions, including *RAS*- and *TET2* mutations, have recently been identified in advanced SM. In patients with SM-AHNMD, such additional lesions are often detectable in the 'AHNMD-component' of the disease. Clinically relevant symptoms of SM result from i) malignant MC infiltration and the subsequent organ damage seen in advanced SM and/or ii) the release of pro-inflammatory and vasoactive mediators from MC, found in all disease-variants. Therapy of SM has to be adjusted to the individual situation in each patient. In ISM, the aim is to control mediator release and mediator effects. In advanced SM, a major goal is to control MC expansion by using conventional drugs or novel targeted drugs directed against mutant forms of *KIT* and/or other pro-oncogenic kinase-targets. In rapidly progressing ASM, MCL and drug-resistant AHNMD, chemotherapy and subsequent stem cell transplantation has to be considered.

**Keywords:** Mastocytosis, mast cells, rare disease, *KIT* mutations, targeted therapy

## Introduction

Mastocytosis is a group of rare clonal disorders characterized by abnormal expansion and accumulation of tissue mast cells (MC) in the skin and/or in visceral organs [1-10]. Depending on the affected organ(s), mastocytosis can be divided into cutaneous mastocytosis (CM), systemic mastocytosis (SM), and localized MC tumors [1-15]. The classification of the World Health Organization (WHO) discriminates between several distinct subvariants of CM and SM [11-15]. The prognosis and the clinical course vary greatly among these patients [11-18]. Moreover, mastocytosis patients complain about symptoms caused by diverse MC-derived mediators, especially when these patients also suffer from an allergic disease [19-24]. Mediator-related symptoms may be mild, extensive or even life-threatening [19-24]. In those with severe anaphylaxis, a so-called MC-activation syndrome (MCAS) is often diag-

nosed [22-24]. Patients with SM may also suffer from osteopathy, gastrointestinal problems, neurological or psychiatric symptoms or/and from cutaneous symptoms, such as flushing or pruritus (**Table 1**) [19-21, 25-28]. In patients with advanced SM, additional problems and pathologies, such as a lymphadenopathy, hepato- and/or splenomegaly, liver damage, cytopenia, ascites or malabsorption may occur (**Table 1**) [11-18]. Whereas the prognosis in cutaneous disease (CM) and indolent SM (ISM) is excellent with (almost) normal life-expectancy, the prognosis in aggressive SM (ASM) and MC leukemia (MCL) is dismal [15-18]. The current article provides a 'state of the art overview' on the biology, diagnosis, classification and therapy of mastocytosis.

## Incidence and prevalence

Although no exact values on the incidence and prevalence of the disease have been reported

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**Table 1.** Recurrent findings and symptoms in patients with systemic mastocytosis (SM)

Findings/symptoms	typically seen in patient with	
	indolent SM	advanced SM*
Skin involvement (MIS)	+/-**	-/+**
Leukocytosis	-	+/-
Eosinophilia	+/-	+
Circulating mast cells	-	-/+***
Marked cytopenia	-	+
Bone marrow (BM) fibrosis	-/+	+/-
Marked BM dysplasia	-	+/-
Mast cells in BM smears >5%	-	+/-
Serum Tryptase >200 ng/mL	+/-	+
Splenomegaly	-/+	+
Lymphadenopathy (abdominal)	-/+	+/-
Hepatopathy with ascites	-	+
Elevated alkaline phosphatase	-	+
Large osteolyses	-	-/+
Osteoporosis	+/-	-/+
Recurrent severe anaphylaxis	+/-	-/+
Hypotension and tachycardia	+/-	+/-
Fever and night sweats	-	-/+
Fatigue	+/-	-/+
Psychiatric or neurologic symptoms	+/-	-/+
Gastrointestinal (GI) crampi	+	+/-
Loose stools or diarrhea	+	+/-
Ulcerative GI tract disease	+/-	+/-
Malabsorption	-	-/+
Weight loss	-	+

\*Advanced SM includes aggressive SM (ASM) and mast cell leukemia (MCL).

\*\*In most adult patients with indolent SM (ISM), urticaria pigmentosa-like skin lesions are found. Those who have indolent SM but do not exhibit skin lesions, are classified as (isolated) bone marrow mastocytosis (BMM). In these cases, it is important to exclude advanced SM, a condition that is typically presenting without skin lesions (>50% of cases). \*\*\*Circulating mast cells are typically found in patients with classical MCL. Abbreviations: MIS, mastocytosis in the skin; BM, bone marrow. +, frequently seen; +/-, found in a subset of patients; -/+, rarely seen; -, not found.

to date, mastocytosis is considered a rare disease. However, during the past 2 decades, the number of well-documented cases and thus the incidence of mastocytosis increased substantially in the Western world (US and Europe). This is most probably due to better diagnostics, increased awareness in the public, and an increasing knowledge of physicians. The estimated prevalence of mastocytosis in Middle Europe is 0.005-0.01% or 0.5-1 per 10,000. No apparent gender predominance has been reported. Most patients are children and suffer from cutaneous mastocytosis (CM). In many of these patients, overt signs of mastocytosis disappear shortly before, during or shortly after puberty [6-12, 21]. Although rare forms of familial mastocytosis (about 50-100 families worldwide) and predisposing gene-polymorphisms have been described, typical mastocytosis is considered a non-hereditary somatic

disease [4-14]. In many cases, mastocytosis remains undetected for many years (occult mastocytosis). Robust registries for the disease have not been established so far, which is a clear unmet need and explains why no detailed epidemiologic data have been published so far.

### Biology, history and classification

Mast cells (MC) are myeloid cells that express histamine and other pro-inflammatory mediators in their granules, and bear high-affinity binding-sites for IgE [29, 30]. Similar to other leukocytes, MC are constantly replenished from a pool of pluripotent and committed hematopoietic progenitor cells [29-31]. MC progenitor cells express the tyrosine kinase receptor KIT [29-32]. The ligand of this oncogenic receptor, stem cell factor (SCF), induces MC development in uncommitted and MC-committed hematopoietic precursor cells [31-33]. However, in patients with mastocytosis, SCF-independent development, expansion and accumulation of MC is seen [6-10]. Historically, mastocytosis was first described as a skin disease named urticaria pigmentosa, UP [34]. Indeed, most patients

present with typical skin lesions. However, absence of cutaneous lesions does not exclude the presence of SM.

The classification of mastocytosis stems back to 1949, when a first case of mastocytosis with internal organ-involvement was described [35]. Between 1950 and 1975, several different variants of SM, including a leukemic variant, MCL, were reported. A first comprehensive classification-proposal was presented by Karl Lennert and the Kiel group in 1979 [1]. Later, in 1991, a similar classification-proposal was published by Dean Metcalfe [2]. Between 1990 and 2000, a number of clinical, histomorphological, immunological, and biochemical markers of CM and SM were established [36-42]. In the 'Year-2000 Working Conference on Mastocytosis' the most reliable disease-associated parameters were discussed and finally

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**Table 2.** Classification of Mast Cell Disorders (Mastocytosis)

Variant	Abbreviation	Subvariants
Cutaneous Mastocytosis	CM	- Urticaria Pigmentosa (UP) = Maculopapular CM (MPCM) - Diffuse CM (DCM) - Mastocytoma of Skin
Indolent Systemic Mastocytosis	ISM	- (Isolated) Bone Marrow Mastocytosis (BMM)
Smoldering Systemic Mastocytosis	SSM	
Systemic Mastocytosis with an Associated clonal Hematologic Non Mast Cell Lineage Disease	SM-AHNMD	- SM-AML - SM-MDS - SM-MPN - SM-CMML* - SM-CEL** - SM-NHL
Aggressive Systemic Mastocytosis	ASM	- Lymphadenopathic SM with Eosinophilia
Mast Cell Leukaemia	MCL	- Typical MCL - Aleukemic Variant of MCL
Mast Cell Sarcoma	MCS	
Extracutaneous Mastocytoma		
Myelomastocytic Leukemia	MML	- Aleukemic variant of MML
Mast Cell Activation Syndrome	MCAS	- Primary MCAS - Secondary MCAS - Idiopathic MCAS

### Mast Cell Hyperplasia

\*SM-CMML is the most frequent form of SM-AHNMD. \*\*In a subset of patients with SM-CEL, FIP1L1/PDGFR $\alpha$ , but no KIT D816V, is found. In each case of SM-AHNMD, both the SM variant and the AHNMD variant of the disease has to be established by using WHO criteria. Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; CMML, chronic myelomonocytic leukemia; CEL, chronic eosinophilic leukemia; NHL, Non-Hodgkin's lymphoma.

selected as official criteria to define mastocytosis and to delineate variants of CM and SM [11]. The resulting consensus was adopted by the WHO and served as official classification of mastocytosis in 2001 [12], and later, in 2008, this classification was reconfirmed [14]. Based on this classification, the following disease variants are defined: ISM, SM with an associated hematologic non-MC-lineage disease (SM-AHNMD), aggressive SM (ASM), and MCL. As mentioned above, the clinical picture, course and prognosis vary greatly among these variants. The smoldering type of SM (SSM) was initially described as a 'sub-entity' of ISM [11]. However, in 2007, the EU-US consensus group described this condition as a definitive variant of SM [21]. A currently proposed global classification of mast cell diseases is shown in **Table 2**.

Between 2002 and 2013, the consensus group continued to work on markers, criteria, and standards, in order to improve diagnosis, staging and prognostication in CM and SM, and to formulate treatment response criteria [15, 21-23, 43]. In 2002, the European Competence Network on Mastocytosis (ECNM) was initiated [44, 45]. The major aim of this academic net-

work is to provide the most recent information to doctors and patients, and to improve diagnosis and therapy in mastocytosis [44, 45].

### Diagnostic criteria

Minimal diagnostic criteria of CM and SM, proposed by the consensus group and the WHO, are widely used and generally accepted. CM is defined by typical skin lesions detected by inspection (macroscopy), a 'positive' histology, and absence of criteria sufficient to diagnose SM [11, 14-21]. It is important to know that a minimal infiltration of the bone marrow by neoplastic MC is often 'subdiagnostic' regarding SM, so that the final diagnosis remains CM in these cases [11-14, 21]. Even in patients in whom two minor SM criteria are fulfilled, the diagnosis remains CM [11-14]. The major SM criterion is a histologically confirmed infiltration of MC in one or more extracutaneous (visceral) organs. In most patients, the bone marrow (BM) is examined. The recommended stains for detection and enumeration of MC and MC infiltrates in the BM (and all other organs) are KIT (CD117) and tryptase [11-14, 40]. In typical cases of SM, smaller or/and larger compact infiltrates of spindle-shaped MC are found in

**Table 3.** Diagnostic Criteria for Systemic Mastocytosis (SM)

Major:*	Multifocal dense infiltrates of MC in bone marrow sections or other extracutaneous organ(s) (>15 MCs in aggregate)
Minor:*	<ul style="list-style-type: none"> <li>i. MC in bone marrow or other extracutaneous organ(s) show an abnormal (spindle-shaped) morphology (&gt;25%)</li> <li>ii. <i>KIT</i> mutation at codon 816** in extracutaneous organ(s)</li> <li>iii. MC in bone marrow express CD2 and/or CD25</li> <li>iv. Serum total tryptase &gt;20 ng/ml (does not count in patients who have AHNMD-type disease)</li> </ul>

\*When at least one major and one minor or at least three minor criteria are present, the diagnosis SM is established. \*\*Activating mutations at codon 816 of *KIT*; in most cases, *KIT* D816V is found. Abbreviations: MC, mast cell(s), AHNMD, associated clonal hematologic non mast cell lineage disease.

*KIT*-tryptase-stained BM sections [11-14, 40]. Minor SM criteria include i) an atypical morphology of MC, ii) expression of CD2 or/and CD25 in MC, iii) the presence of *KIT* D816V in the BM or another extracutaneous organ, and iv) a basal serum tryptase level exceeding 20 ng/mL [11-14]. If at least one major and one minor or at least three minor SM criteria are fulfilled, the diagnosis SM is established (**Table 3**). With regard to diagnostic algorithms, assays and standards used in daily practice, we refer to the available literature [11-14, 21, 22]. An important aspect is that most patients with CM are children, whereas in most adult patients, SM is diagnosed. Therefore, in children, no BM biopsy is required unless clear signs for advanced SM or an AHNMD are found [21]. By contrast, in adults, a BM biopsy is always required in order to establish the final diagnosis [11-14, 21]. In adult patients who present with skin lesions but refuse a BM biopsy, the provisional diagnosis of 'mastocytosis in the skin' (MIS) is appropriate [21], whereas the traditional way to diagnose CM in such cases is obsolete and should be avoided.

### Molecular features and target antigens

Mastocytosis is a group of clonal myeloid neoplasms defined by factor-independent expansion of neoplastic MC. The key molecular lesions recurrently detected in patients with mastocytosis, are activating *KIT* mutations that may explain the autonomous growth and expansion of neoplastic MC [10, 37, 38, 42, 46-48]. In pediatric patients with CM, a number of different *KIT* mutations, including *KIT* D816V, have been identified [10, 46-48]. By contrast, in most adult patients suffering from SM, the *KIT* mutation D816V is detected, independent of the variant of SM [10-14, 37, 38, 42]. The fact that in all these patients, including cases with ISM, who have a (near) normal life-expec-

tancy, neoplastic MC display *KIT* D816V, is remarkable, and points to additional mechanisms and molecular defects responsible for disease progression in ASM and MCL. In other words, manifestation of an AHNMD, of ASM or of MCL, cannot be explained by *KIT* D816V alone, but is likely to result from additional factors. Indeed, recent data suggest that a number of additional lesions are detectable in patients with SM-AHNMD, ASM and MCL. These lesions include *RAS* mutations, *TET2* mutations, mutations in *IgE receptor* genes and other genes [49-52].

A summary of molecular lesions typically found in advanced SM is shown in **Table 4**. A special condition is SM-AHNMD. Here, a number of different disease variants and related molecular lesions, have been identified [53-57]. In most patients, an associated myeloid malignancy is diagnosed [53-57]. By contrast, lymphoid variants of AHNMD, such as a multiple myeloma, are rarely found. In some cases, hypereosinophilia occurs. In these patients, chronic eosinophilic leukemia (CEL) may be diagnosed. In rare cases, the *FIP1L1/PDGFR* fusion gene is detectable [58-60]. However, in these patients, the SM component is usually small and neoplastic cells usually lack *KIT* D816V. Moreover, in most cases of *FIP1L1/PDGFR*+ CEL, the criteria for SM are not fulfilled even if MC are spindle-shaped cells expressing CD25 [59, 60]. In some cases this may be due to the fact that the SM-infiltrates are outnumbered and thus masked by neoplastic eosinophils. The delineation between *FIP1L1/PDGFR*+ CEL and *KIT* D816V+ advanced SM with eosinophilia has important clinical implications. In particular, several different studies have shown that only patients with typical CEL with a rearranged *PDGFR*, but not those with advanced SM exhibiting *KIT* D816V, respond to treatment with imatinib.

**Table 4.** Molecular somatic lesions and abnormalities found in patients with mastocytosis

Molecular Abnormality	Reported in patients with	Estimated frequency in patients with SM	reference #
<i>KIT</i> D816V	all SM variants, rarely in CM	>80%	37, 38, 42
<i>KIT</i> D816Y	CM, ISM, SM-AHNMD	<5%	10, 47, 48
<i>KIT</i> D816F	CM	<5%	10, 47, 48
<i>KIT</i> D816H	MCL, ASM, SM-AHNMD	<5%	10, 47
<i>KIT</i> D820G	ASM	<5%	10, 46
<i>KIT</i> V560G	ISM	<5%	10, 46
<i>KIT</i> F522C	ISM	<5%	10, 47
<i>KIT</i> E839K	CM	<5%	10, 47, 48
<i>KIT</i> V530I	SM-AHNMD	<5%	10, 47
<i>KIT</i> K509I	SM (familial type)	<5%	10, 47, 48
Other <i>KIT</i> mutations	CM and/or SM variants	<5%	10, 47, 48
<i>FIP1L1/PDGFR</i> A	SM-CEL	<5%	58, 59, 60
<i>AML1/ETO</i>	SM-AML with t(8;21)	<5%	53
<i>JAK2 V617F</i>	SM-PMF	<5%	95
<i>RAS</i> mutations	ASM, SM-AHNMD	<5%	51
<i>TET2</i> mutations	SM-AHNMD, ISM, ASM	<5%	49, 50
<i>DNMT3A</i> mutations	ISM, SM-AHNMD	<5%	50
<i>ASXL1</i> mutations	SM-AHNMD	<5%	50
<i>CBL</i> mutations	SM-AHNMD	<5%	50

CM, cutaneous mastocytosis; SM, systemic mastocytosis; SM-AHNMD, SM with an associated haematologic clonal non mast cell lineage disease; CEL, chronic eosinophilic leukemia; AML, acute myeloid leukemia; PMF, primary myelofibrosis.

**Diagnostic algorithm and staging in patients with suspected SM**

In adult patients with histologically confirmed mastocytosis in the skin (MIS), a BM biopsy is recommended, regardless of the serum tryptase level [6, 11, 12, 21]. In adult patients without skin lesions who are suffering from typical mediator-related symptoms, the basal serum tryptase level is an important ‘preinvasive’ screen parameter. In patients who have a clearly elevated basal serum tryptase level, a BM biopsy should be performed [21]. It is of great importance to know that the serum tryptase increases transiently during an anaphylactic episode [8, 21, 22, 61, 62]. In these patients, serum samples for basal serum tryptase measurements should be collected at least 48 hours after complete resolution of all anaphylaxis-related symptoms [21]. Another useful screen approach is the examination of peripheral blood cells for the presence of *KIT* D816V by a highly sensitive test. The presence of *KIT* D816V is highly indicative for the presence of SM.

In patients with known SM, a number of different staging investigations need to be performed. BM investigations include BM smears (Wright-Giemsa-stained), histology and immunohistochemistry, cytogenetics, PCR to detect *KIT* D816V, and flow cytometry if available [6, 11-14, 21, 39]. Flow cytometry should be per-

formed in order to document expression of CD2 and/or CD25 on neoplastic MC [21, 39]. However, today, expression of CD25 in BM MC can also be demonstrated easily by immunohistochemistry (IHC) [63, 64]. With both staining methods (flow and IHC), CD25 is the more sensitive and specific diagnostic approach [64]. Peripheral blood investigations include a complete blood count with (microscopic) differential counts, blood chemistry, including serum tryptase, calcium, alkaline phosphatase, coagulation parameters, total IgE, and allergy-diagnostics. Further staging examinations include an osteodensitometry (T Score by DEXA-Scan), X ray of bones, X ray of thorax, and an abdomen ultrasound [11-14, 21]. In those patients who have a decreased T Score, a yearly DEXA-Scan is recommended. In select cases, additional investigations, such as a CT scan, may be required. It is important to note that these investigations are appropriate in adulthood mastocytosis, whereas in children, most of these staging investigations are usually not required. Notably, in most children with MIS, only the peripheral blood and spleen size are examined, whereas all other staging investigations are usually not performed as significant systemic involvement is rarely seen [21].

**Differential diagnoses**

A number of differential diagnoses have to be considered in patients with suspected SM,

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**Table 5.** Hematologic Disorders as Major Differential Diagnoses of SM

Clinical Findings/Features	Major Differential Diagnoses
Cytopenia + Elevated Tryptase*	Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML)
Thrombocytosis and/or BM fibrosis and Splenomegaly + Elevated Tryptase*	Primary Myelofibrosis (PMF), Essential Thrombocythemia (ET), RARS-T
Leukocytosis + Eosinophilia + Elevated Tryptase*	CEL, CML, AML-M4eo, PDGFR- or FGFR-rearranged Neoplasms
Leukocytosis with an increase in blast cells + Elevated Tryptase*	Tryptase+ AML, CML blast phase (BP)
Increase in Circulating Metachromatic Cells	Chronic Myeloid Leukemia (CP or AP) Myelomastocytic Leukemia (MML) Chronic Basophilic Leukemia
Lymphadenopathy and Hepato/Splenomegaly	Malignant Lymphoma (NHL) and Morbus Hodgkin**
Huge Osteolyses with Bone Fractures + Osteoporosis + Elevated Tryptase***	Multiple Myeloma***

SM, systemic mastocytosis; RARS-T, refractory anemia with ring sideroblasts and thrombocytosis; CEL, chronic eosinophilic leukemia; CP, chronic phase; AP, accelerated phase; NHL, Non-Hodgkin's Lymphoma. \*A serum tryptase level exceeding 20 ng/ml is usually found in patients with a myeloid neoplasm. In some patients with AML, serum tryptase levels may increase to >500 ng/ml. \*\*Neoplastic cells in advanced SM usually express CD30 (Ki-1), a marker that is otherwise specifically expressed in lymphoma cells in patients with Morbus Hodgkin and Anaplastic Large Cell Lymphoma. \*\*\*In some patients with SM, a paraproteinemia may be detected, and in a (very) few patients, an overt multiple myeloma (MM) develops (SM-MM); however, osteopathy in SM usually develops independent of paraproteinemia.

especially when typical skin lesions (MIS) are not present. In fact, mediator-related symptoms are also recorded in patients with allergies, atopic patients or patients who are intolerant against certain drugs, food, plants or metals. In addition, a number of different internal disorders, neurologic or psychiatric diseases, and other conditions, can mimic MC-mediator-induced symptoms. A summary of relevant 'hematologic' differential diagnoses are shown in **Table 5**.

In patients with cytopenia(s) and elevated serum tryptase levels, a number of hematologic neoplasms have to be considered. These include, among others, myelodysplastic syndromes (MDS), primary myelofibrosis (PMF), and acute myeloid leukemia (AML) [65-68]. In those with eosinophilia, the presence of CEL has to be considered. An increase in immature metachromatic cells in the peripheral blood may be a diagnostic challenge. In these patients, acute or chronic basophilic leukemia has to be excluded. Chronic myeloid leukemia (CML) typically presents with basophilia. In advanced CML, massive basophilia, including immature forms, may be detected. It is of importance to note that contrasting the morphology of mature cells, immature basophils are mononuclear cells, whereas immature mast cells often exhibit bi- or multi-lobed nuclei

(so-called 'promastocytes') [41]. In cases presenting with immature metachromatic blasts (metachromatic blasts) it is usually impossible to differentiate between MC and basophils. In these patients, immunophenotyping and electron microscopy is required to define the type (lineage) of the affected cell [66, 69, 70]. A classification of metachromatic cells detectable in patients with MC disorders is shown in **Table 6**. One important differential diagnosis to MCL is myelomastocytic leukemia (MML) [69-71]. In these patients, metachromatic blasts and promastocytes are detectable and often represent the predominant population of cells.

### Treatment options in indolent SM

In many patients with SM, no relevant symptoms occur, even when observed over years. However, because of the risk of unexpected severe anaphylaxis, prophylactic histamine receptor antagonists are usually recommended [6, 11, 21]. The basis of therapy in SM is a combination of an H1- and H2 histamine receptor antagonist [6, 11, 21]. In case of severe GI-tract symptoms, a proton pump-inhibitor (PPI) should be added [11, 21]. Such PPI should not be used without a H2 histamine receptor blocker in these patients, however. In patients with anaphylaxis or other severe mediator-related symp-

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**Table 6.** Morphologically defined subsets of mast cells found in bone marrow smears in patients with mastocytosis

Cell type	Morphological Features/Criteria
Metachromatic blast	blast cell with a few metachromatic granules
Promastocyte = Atypical MC type II	mature or immature mast cells with bi- or multi-lobed nuclei, often hypogranulated
Atypical MC type I	mast cells exhibiting 2 or 3 of the following three morphological criteria: i. cytoplasmic extensions (spindle shape) ii. hypogranulated cytoplasm iii. oval decentralized nucleus
Mature MC = typical tissue MC	round cell with round central nucleus and well granulated cytoplasm

MC, mast cell(s).

toms despite antihistamines, additional glucocorticosteroids may be required. In addition, MC-stabilizing agents are sometimes used to treat mediator-related symptoms in these patients. Some of the novel TKI, such as dasatinib and midostaurin, have been described to block IgE-dependent histamine release [72, 73]. Whether these effects are relevant clinically remains at present unknown.

Osteopathy is another important clinical feature in ISM that needs attention and often requires therapy. Especially those patients who are treated with glucocorticosteroids have a rather high risk to develop osteoporosis. Repeated DEXA-Scan studies (evaluation of T score) is recommended for all patients with SM. In those in whom the T score is below -2, bisphosphonates should be considered [21, 74]. Overt osteoporosis (T score <-2.5) is a major challenge in the management of SM. In many cases, pathologic fractures are found despite continuous treatment with bisphosphonates. Additional treatment with low-dose interferon-alpha has been proposed for these patients, but responses are only seen in a subgroup of patients.

A major clinical challenge in SM are co-existing allergic diseases. Notably, in patients with SM, the risk for severe life-threatening anaphylaxis is very high [75-78]. Therefore, all patients with SM are advised to avoid all known (and potential) triggers, and to carry an epi-pen self-injector [5, 8, 21]. Certain allergies seem to correlate with severe anaphylaxis in patients with SM. The most famous example is allergy to bee and wasp venom [75-80]. Therefore, all patients with documented allergy against hymenoptera venom should undergo specific immunotherapy

[81-83]. Depletion of IgE has also been discussed as a potential therapeutic manoeuvre in SM with severe anaphylaxis, but the value of this approach remains questionable. All patients with SM who suffer from a co-existing allergy should be managed and treated in a specialized allergy center, if possible.

### Treatment options in advanced SM

Advanced SM is a term used to denote the following categories of SM: SSM, SM-AHNMD, ASM, and MCL [11-14]. These entities differ substantially from each other in terms of course and prognosis. Therefore, it is of great importance to establish the correct final diagnosis before establishing a treatment plan. In most patients with SSM, no therapy is required. However, these patients may suffer from mild anemia or other signs of incipient ASM. In addition, SSM patients may suffer from severe repeated (life-threatening) anaphylaxis. In these cases, the high burden of MC may be a decisive factor, and cytoreductive therapy may be required to reduce the risk of repeated life-threatening anaphylactic events. A number of case-reports and smaller case series suggest that treatment with cladribine (2CdA) is followed by a substantial and long-lasting decrease in the MC burden (and of serum tryptase levels) in patients with SSM, and that this therapy lowers the risk of fatal anaphylaxis in these patients [84-86]. However, not all patients with SSM may respond to 2CdA [84, 85].

In patients with SM-AHNMD, the prognosis and course is usually determined by the AHNMD component of the disease, even if ASM is diagnosed (ASM-AHNMD) [5-8, 16-18, 53]. In each

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**Table 7.** Cytoreductive treatment and Targeted Drugs in Patients with SM

Disease variant	Treatment options
Indolent Systemic Mastocytosis (ISM)	No cytoreductive treatment is required
Smouldering Systemic Mastocytosis (SSM)	'Watch-and-wait' in most cases. In select cases: IFN- $\alpha$ 2b+glucocorticosteroids or 2CdA.
SM-AHNMD	Treat AHNMD as if no SM was diagnosed and treat the SM-component of the disease as if no AHNMD was found.
Examples:	
1) ISM-CEL with FIP1L1/PDGFR $\alpha$	Imatinib (low dose: 100 mg per day) to control the AHNMD-type of disease (CEL)
2) ISM-AML	Chemotherapy followed by allogeneic stem cell transplantation if possible.
Aggressive Systemic Mastocytosis (ASM) with slow progression	IFN- $\alpha$ 2b+glucocorticosteroids, 2CdA, if resistant: experimental TKI (midostaurin/PKC412) or other experimental drugs/chemotherapy or hydroxyurea.
ASM with rapid progression and patients who do not respond to IFN and 2CdA	Polychemotherapy (CT), consider allogeneic stem cell transplantation in responding patients. If CT does not work: experimental therapy with a TKI (PKC412), 2CdA or other cytoreductive drugs. Hydroxyurea.
Mast cell leukaemia (MCL)	Polychemotherapy followed by allogeneic stem cell transplantation (SCT) if possible. If CT and SCT can not be performed: 2CdA or experimental TKI, such as PKC412. Hydroxyurea is used as palliative drug.

IFN- $\alpha$ 2b, Interferon-alpha2b; SM-AHNMD, Systemic Mastocytosis with an associated. Hematologic clonal Non Mast Cell Lineage Disease; TKI, tyrosine kinase inhibitor.

case it is important to classify both the SM component and the AHNMD type by WHO-criteria, in order to establish a robust treatment plan for these patients [5-8, 10-14, 21, 53]. In general, the SM component of the disease should be treated as if no AHNMD was diagnosed and the AHNMD should be treated as if no SM was present [11-14, 21]. However, there are a number of pitfalls and aspects one should consider when treating a patient with SM-AHNMD using cytoreductive agents. Likewise, in SM-AML, the leukemia must be regarded as secondary AML, and the prognosis of these patients is unfavorable and comparable to that of other patients with secondary AML [87]. In these patients, more intensive therapy (+/- stem cell transplantation) has to be considered (**Table 7**). It is also important to mention that in most patients suffering from a so-called 'AML with KIT D816V', a concomitant SM is detectable if a thorough histologic investigation is performed (otherwise SM is just overlooked) [87, 88]. Another important condition is SM with associated eosinophilia (SM-eo). In these patients, a thorough molecular investigation is required [58-60]. In some of these patients, a rearranged *PDGFR $\alpha$*  but no *KIT D816V* is detectable [58-60]. These

patients often respond to imatinib, whereas patients with *KIT D816V*+ SM with eosinophilia show no response to imatinib, because the *KIT* mutant confers resistance.

In patients with ASM, cytoreductive therapy is almost always required. In those who have a slowly progressing type of ASM, interferon-alpha plus prednisolone or cladribine (2CdA) is recommended [11, 21, 89-91]. However, only a subset of these patients show a long-lasting response [89-91]. In patients who have or develop resistance or who are suffering from rapidly progressing ASM, chemotherapy is required. In young patients who are fit and have a suitable donor, allogeneic stem cell transplantation should be considered (**Table 7**). In elderly patients and those who refuse a stem cell transplant, induction and repeated consolidation cycles of chemotherapy should be applied. The regimens are the same as that used to treat secondary (high risk) AML. One frequently used protocol is the FLAG (fludarabin + ARA-C + G-CSF) regimen. An alternative option is to use experimental drugs such as PKC412 (midostaurin), and hydroxyurea is commonly used as a palliative drug to control MC expansion in advanced SM.



In patients with MCL, the same strategy is followed as in ASM. However, most cases with MCL show rapid progression [6-16, 41, 92-94]. Without chemotherapy, the life expectancy in MCL is less than 1 year [6-16, 41, 92-94]. In those who have a suitable donor, allogeneic stem cell transplantation should be considered. A special condition is MC sarcoma (MCS). Most of these patients progress to MCL within a relatively short time period. Radiation and chemotherapy is usually recommended. However, despite intensive therapy, most patients die after several weeks or months.

### Summary and future perspectives

Mastocytosis is a rare and heterogeneous disease defined by pathologic expansion and accumulation of clonal MC in various organs. In most adult patients, the systemic form of the disease is diagnosed. Whereas the serum tryptase level and KIT D816V in the peripheral blood are useful screen parameters, a bone marrow examination as well as subsequent staging is always required to establish the final diagnosis and subvariant in these patients. Diagnosis and the treatment plan have to be based on a multidisciplinary approach in all patients. In fact, the course of disease and prognosis as well as treatment options vary greatly among SM variants. The final treatment plan has to be adapted to the individual situation in each case. This plan should also take the presence of comorbidities and molecular targets into account. In the past few years, a number of new treatment approaches have been developed for indolent and advanced SM. There is hope for the future that these new concepts can be translated into clinical practice as currently mastocytosis remains an incurable and often resistant disease.

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