

Advances in the Classification and Treatment of Mastocytosis: Current Status and Outlook toward the Future

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Abstract

Mastocytosis is a term used to denote a heterogeneous group of conditions defined by the expansion and accumulation of clonal (neoplastic) tissue mast cells in various organs. The classification of the World Health Organization (WHO) divides the disease into cutaneous mastocytosis, systemic mastocytosis, and localized mast cell tumors. On the basis of histomorphologic criteria, clinical parameters, and organ involvement, systemic mastocytosis is further divided into indolent systemic mastocytosis and advanced systemic mastocytosis variants, including aggressive systemic mastocytosis and mast cell leukemia. The clinical impact and prognostic value of this classification has been confirmed in numerous studies, and

its basic concept remains valid. However, refinements have recently been proposed by the consensus group, the WHO, and the European Competence Network on Mastocytosis. In addition, new treatment options are available for patients with advanced systemic mastocytosis, including allogeneic hematopoietic stem cell transplantation and multikinase inhibitors directed against KIT D816V and other key signaling molecules. Our current article provides an overview of recent advances in the field of mastocytosis, with emphasis on classification, prognostication, and emerging new treatment options in advanced systemic mastocytosis. *Cancer Res*; 77(6); 1261–70. ©2017 AACR.

Introduction and Historical Overview

Mastocytosis is a heterogeneous group of neoplastic conditions characterized by expansion and accumulation of clonal (neoplastic) mast cells (MC) in the skin and various internal organs, such as the bone marrow, spleen, lymph nodes, and the gastrointestinal (GI) tract (1–4). Cutaneous involvement is

found in most patients. A first description of the typical (pigmented) skin lesions was provided by Nettleship and Tay in 1869. A few years later, the term urticaria pigmentosa was coined, and following Paul Ehrlich's description of MCs in 1879, the presence and accumulation of MCs in urticaria pigmentosa lesions was recognized by Unna in 1887 (Table 1). For many

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This manuscript is dedicated to the pioneering work and scientific achievements of Paul Ehrlich (1854–1915) on the occasion of his 100th death anniversary.

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Table 1. Milestones in the history of mast cell and mastocytosis research

Year	Author(s)	Discovery – Achievement
1869	Edward Nettleship and Warren Tay	Rare form of persistent/pigmented urticaria described
1878	Alfred Sangster	Urticaria pigmentosa (UP) term proposed
1879	Paul Ehrlich	Tissue mast cells (MCs) described and named
1887	Paul Gerson Unna	MCs in UP lesions demonstrated
1890~	Ferdinand-Jean Darier	Darier's sign described
1949	John M. Ellis	Systemic mastocytosis described (autopsy case)
1966-1970	Kimishige Ishizaka and Teruko Ishizaka	Reaginic antibody (IgE) detected and linked to IgE-dependent MC activation by allergens
1967-1968	S.G.O. Johansson and Hans Bennich	Discovery of an IgE myeloma and development of tests for measuring IgE levels in biological fluids
1977	Yukihiko Kitamura	MCs derive from hematopoietic stem cells
1978/1979	Yukihiko Kitamura	<i>W/W^u</i> and <i>Sl/Sl^d</i> mice are MC-deficient
1979	Karl Lennert	Kiel classification includes mastocytosis
1987	Lawrence B. Schwartz	Acute serum tryptase elevation indicates MC activation
1988	Joseph H. Butterfield	First human MC line, HMC-1, established
1988	Multiple Researchers	<i>KIT</i> is encoded by <i>W</i> locus of mice
1989	Peter Valent	Specific immunophenotype of human MCs
1990	Multiple Researchers	SCF is encoded by <i>Sl</i> locus of mice
1991	Dean Metcalfe	Consensus classification of mastocytosis
1992	Multiple Researchers	SCF is a growth factor for human MCs
1993	Takuma Furitsu and Yukihiko Kitamura	<i>KIT</i> D816V detected in HMC-1 cells
1995	Hiroshi Nagata and Dean D. Metcalfe	<i>KIT</i> D816V detected in patients with SM
1995	Lawrence B. Schwartz	Basal serum tryptase level reflects MC burden
1998	Hans-Peter Horny	Tryptase immunohistochemistry to detect neoplastic MC infiltrates in bone marrow
1998	Luis Escribano	Abnormal MC phenotype (CD2 ⁺ and CD25 ⁺) on MCs in patients with SM
2000	Multiple Researchers	Year 2000 working conference on mastocytosis: consensus criteria & classification proposed
2001	WHO Group	WHO classification of mastocytosis established based on year 2000 working conference proposal
2001	Wolfgang R. Sperr	Morphologic subsets of neoplastic mast cells
2002	Peter Valent	European Competence Network on Mastocytosis (ECNM) founded
2003-2007	Consensus Group	Standardization and response criteria for mastocytosis established and updated
2008	WHO Group	Updated WHO classification
2010	Cem Akin	Definition and criteria for mast cell activation syndrome (MCAS) proposed
2011	Karl Sotlar	CD30 expression in neoplastic mast cells
2012	Consensus Group	Global consensus classification of mast cell disorders including MCAS
2016	WHO Group	Updated WHO classification
2016	Jason Gotlib	First successful trial with a multi-kinase/ <i>KIT</i> inhibitor (midostaurin) in patients with advanced SM including MCL

Abbreviations: IgE, immunoglobulin E; IgE-R, IgE receptor; SM, systemic mastocytosis.

years, mastocytosis was believed to be a disease of the skin. However, in 1949, Ellis described a first case of systemic mastocytosis (Table 1). Over time since this observation, systemic mastocytosis has become a well-recognized diagnostic entity, although other patients were found to have urticaria pigmentosa without systemic involvement. These patients, mostly children, are classified as cutaneous mastocytosis and have a good prognosis (5). A localized form of cutaneous mastocytosis, termed mastocytoma of skin, has also been described (6, 7). Overall, the basic classification of mastocytosis into cutaneous and systemic remains valid. However, during the past 30 years, a number of clinically and prognostically distinct subvariants of cutaneous mastocytosis and systemic mastocytosis have been described (8–10). Between 1991 and 2000, novel robust criteria of systemic mastocytosis were established (11–19). These criteria were discussed extensively before and during a Working Conference in 2000, from which an updated consensus classification was proposed by the EU-US consensus group (20). This proposal was adopted by the World Health Organization (WHO) in 2001 (21) and was updated and reconfirmed in 2008 (22).

WHO Criteria and Classification of Mastocytosis 2001-2016

The WHO classification divides cutaneous mastocytosis into maculopapular cutaneous mastocytosis (MPCM), also known as urticaria pigmentosa, diffuse cutaneous mastocytosis (DCM), and localized mastocytoma of skin. Specific criteria of cutaneous mastocytosis have been defined and published by the consensus group (23, 24). Most patients with cutaneous mastocytosis are children. In contrast, in most adult patients, systemic mastocytosis is detected. The major criterion of systemic mastocytosis is the multifocal accumulation and clustering of MCs (at least 15/cluster) in the bone marrow or another extra-cutaneous organ (20–22). Minor systemic mastocytosis criteria confirm the clonal (neoplastic) nature of the disease and include an abnormal MC morphology (spindling), expression of CD2 and/or CD25 in MCs in extracutaneous organs, expression of an activating mutation in codon 816 of *KIT* (usually *KIT* D816V) in extra-cutaneous cells, and a basal serum tryptase level exceeding 20 ng/mL (Supplementary Table S1; refs. 20–22). When the major systemic mastocytosis criterion and at least one minor systemic mastocytosis

criterion or 3 minor systemic mastocytosis criteria are fulfilled, the diagnosis of systemic mastocytosis is established (Supplementary Table S1).

A number of attempts have been made to define and standardize diagnostic markers and laboratory approaches in cutaneous mastocytosis and systemic mastocytosis and to develop diagnostic algorithms (23–27). Recommended parameters to screen for systemic mastocytosis include an elevated baseline serum tryptase and detection of *KIT* codon 816 mutations in peripheral blood leukocytes using a highly sensitive allele-specific PCR test (23, 26–31). A thorough bone marrow investigation is recommended in adult patients who have a clearly elevated tryptase, a *KIT* (codon 816) mutation, or typical clinical symptoms, such as pruritus, flushing, GI cramping, diarrhoea, anaphylaxis to bee or wasp venom, or osteoporosis (23, 26). An accumulation of such findings increases the likelihood of systemic mastocytosis. A diagnostic algorithm incorporating such observations and parameters has been published recently by the consensus group (26).

Systemic mastocytosis is further divided into indolent systemic mastocytosis (ISM), systemic mastocytosis with an associated clonal hematologic non-MC-lineage disease (SM-AHNMD), aggressive systemic mastocytosis (ASM), and MC leukemia (MCL) (Supplementary Table S2; refs. 20–22). In ISM, two provisional subvariants have been described: (i) a variant where the disease is essentially restricted to the bone marrow and the tryptase level is low or normal, termed isolated bone marrow mastocytosis (BMM); and (ii) a variant where the burden of MCs in internal organs is high and the neoplastic (*KIT* mutant-triggered) process expands to other myeloid lineages, termed smoldering systemic mastocytosis (SSM; refs. 20–22). In 2007, SSM was designated as a separate variant of systemic mastocytosis by the consensus group (23), and since 2016, SSM is also a separate WHO category of systemic mastocytosis (32, 33). Repeated studies have confirmed the prognostic impact of the WHO classification regarding the survival of patients with systemic mastocytosis (19, 34–37). Thus, whereas patients with ISM have a normal or near normal life-expectancy, the prognosis (survival) is poor in advanced systemic mastocytosis. With the exception of skin mastocytomas, localized MC neoplasms, including MC sarcomas (MCS), are extremely rare (38–41).

WHO Update 2016 and Justification

Several adjustments have been introduced in the 2016 update of the WHO classification of mastocytosis (Table 2; Supplementary Table S3; refs. 32, 33). First, the smoldering subtype of systemic mastocytosis (SSM), a provisional entity of ISM in previous WHO proposals, is now considered a distinct category of systemic mastocytosis by the WHO. The prognosis in SSM regarding progression-free and overall survival is better than that in ASM or MCL, but is still poor when compared with typical ISM (excluding SSM). It is noteworthy that each B-Finding (criteria of SSM) by itself, including organomegaly, high tryptase level (>200 ng/mL), and evidence of clonal involvement of non-MC lineages, indicates a poor prognosis (35, 42–46).

In the WHO classification 2016, the extremely rare "extracutaneous mastocytoma" has been removed (Table 2; Supplementary Table S3; refs. 32, 33) as with one recent excep-

Table 2. Updated WHO classification of mastocytosis 2016

Cutaneous mastocytosis (CM)
- Maculopapular CM (MPCM) = urticaria pigmentosa (UP)
- Diffuse CM (DCM)
- Mastocytoma of skin
Systemic mastocytosis (SM)
- Indolent SM (ISM)
- Smoldering SM (SSM)
- SM with associated hematologic neoplasm (AHN) ^a
- Aggressive SM (ASM)
- Mast cell leukemia (MCL)
Mast cell sarcoma (MCS)

^aThe previous term SM-AHNMD (systemic mastocytosis with clonal hematologic non-mast cell-lineage disease) and the new term AHN can be used synonymously.

tion (38), no such cases have been published during the past 20 years.

The term AHNMD has been accepted and used for many years, although sometimes thought to be unnecessarily descriptive (20–23). Therefore, the WHO update of 2016 allows and recommends the use of the following new synonym: associated hematologic neoplasm (AHN; Table 2; Supplementary Table S3; refs. 32, 33). Both terms, AHN and AHNMD, may be used interchangeably.

In patients with ASM, the percentage of MCs in the bone marrow smear is of prognostic significance, and those who have 5%–19% MCs in their bone marrow smears may at some point transform to overt MCL (19). Therefore, the consensus group proposed in 2014 that ASM be divided into untransformed disease and ASM in transformation to MCL (47). The proposed terminology for transformed ASM is "ASM-t," and is defined by a MC count of 5%–19% in bone marrow smears (47). The updated WHO classification of mastocytosis is shown in Table 2.

Most Recent Advances in the Classification and Criteria Defining Cutaneous Mastocytosis and Systemic Mastocytosis

Delineation of variants of childhood MPCM (urticaria pigmentosa)

Cutaneous lesions of mastocytosis are present in cutaneous mastocytosis and systemic mastocytosis regardless of age. Most adult patients with typical skin lesions have systemic mastocytosis. In children, cutaneous mastocytosis is usually diagnosed. In many cases, cutaneous lesions disappear before or during puberty. However, in some patients, skin lesions persist into adulthood (5, 24). More recently, two distinct forms of childhood MPCM have been recognized: a variant characterized by monomorphic small-sized lesions, and a second variant defined by polymorphic (often larger) lesions (24, 48). Only the monomorphic form is found in adults, suggesting that only this variant persists into adulthood, whereas polymorphic lesions usually resolve (24, 48). Unexpectedly, there is only a weak correlation between monomorphic lesions and *KIT* D816V (48). In fact, *KIT* D816V is also detected in some cases with polymorphic lesions that may resolve by adulthood, and there are other patients with monomorphic skin infiltrates in whom no *KIT* D816V mutation is found (48).

Diagnostic potential of "non-codon-816" *KIT* mutations

A number of novel *KIT* mutations have been detected in patients with cutaneous mastocytosis and systemic mastocytosis

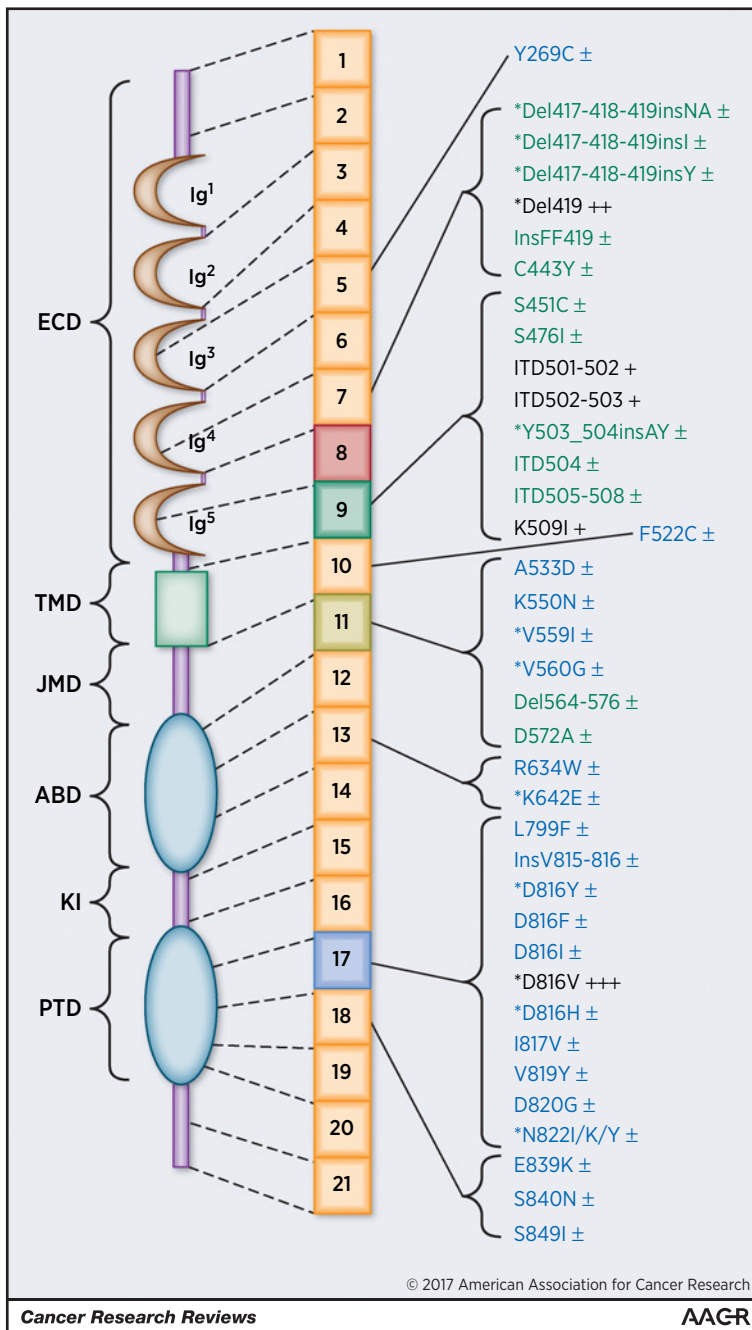


Figure 1.

Overview of *KIT* mutations described in patients with mastocytosis. Mutations described primarily in pediatric cases with cutaneous mastocytosis (CM) are depicted in green and those found preferentially in adults with systemic mastocytosis (SM) in blue. The most frequently detected *KIT* mutations are marked with dark colors (CM, dark green; SM, dark blue). In addition, the frequency of mutations is defined by the following score: ±, found in less than 1% of the pediatric or adult patients; +, found in 1%–5% of pediatric patients; ++, found in 5%–20% of pediatric patients; +++ (*KIT* D816V), mutation found in around 30% of pediatric patients and in >80% of all adult patients. ABD, ATP-binding domain; Del, deletion; ECD, extracellular domain; Ins, insertion; ITD, internal tandem duplication; JMD, juxtamembrane domain; KI, kinase insert; PTD, phosphotransferase domain; TMD, transmembrane domain. The asterisk (*) denotes *KIT* mutations that have also been described in other neoplasms such as gastrointestinal stromal tumors (GIST), acute myeloid leukemia (AML), lymphomas, or seminomas. These neoplasms may also present with other *KIT* mutant forms not yet described in mastocytosis (not shown in this figure). Reproduced in slightly modified form (with permission from the Editors and Publishers) from Arock and colleagues, *Leukemia* 2015;29:1223–32 (ref. 27).

(Fig. 1; refs. 27, 49–52). Some of these mutations, such as K509I, are more common in pediatric cases, sometimes being detected in germline DNA (49–52). Interestingly, several "atypical" *KIT* mutations may facilitate transformation to more advanced disease. Indeed, advanced systemic mastocytosis has been associated with such "atypical" non-D816V *KIT* mutations (Fig. 1; Supplementary Table S4). These *KIT* mutations may play a similar role in disease evolution as *KIT* D816V. Therefore, these mutations may serve as minor systemic mastocytosis criterion in future proposals to diagnose and classify cutaneous mastocytosis and systemic mastocytosis. Another important issue is the method applied to detect *KIT* D816V in the peripheral blood and bone marrow. A

generally accepted recommendation is to employ a highly sensitive, allele-specific, PCR method and to quantify the *KIT* D816V-mutant allele burden in all patients with systemic mastocytosis if possible (27–30, 43, 44).

Does BMM qualify as a separate variant of systemic mastocytosis?

A number of recent studies have shown that BMM is a clinically relevant entity that is often overlooked in clinical practice. In many cases, severe recurrent anaphylaxis, sometimes associated with an IgE-mediated allergy to bee or wasp venom, or unexplained osteoporosis are found (53–55). Cutaneous lesions of

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mastocytosis are typically absent and basal tryptase levels are normal or slightly elevated. Moreover, in most patients with BMM, the *KIT* D816V allele burden in the peripheral blood is low. A bone marrow examination usually reveals small-sized clusters and aggregates of MCs. Sometimes, a well-differentiated (WD) MC morphology is seen. Regarding progression to advanced systemic mastocytosis, the prognosis is good. However, severe or even fatal anaphylaxis may occur. On the basis of these considerations, BMM, now regarded a provisional subcategory of systemic mastocytosis, should probably become a separate variant of systemic mastocytosis. While no detailed diagnostic criteria for BMM have been proposed or agreed upon by a formal consensus conference, we are of the opinion that (i) absence of skin lesions, (ii) a low or normal serum tryptase level, and (iii) absence of B-Findings and C-Findings would be reasonable diagnostic criteria to propose for BMM.

WD morphology of MCs

A unique histopathologic variant of systemic mastocytosis displaying mature MC morphology was described in 2004 (56). Since then, a number of studies have reported a well-differentiated morphology of MCs in a subset of patients with systemic mastocytosis (52, 57–59). Some of the authors have reasoned that this finding should be the basis for a separate category of systemic mastocytosis. However, a well-differentiated MC morphology can occur in many WHO variants of systemic mastocytosis, including BMM, ISM, and MCL. Therefore, it may be appropriate that the well-differentiated morphology be applied broadly as an adjunct to the systemic mastocytosis variant defined by the WHO. Likewise, a patient with ISM with a "WD-morphology" of MCs would be called ISM-WD (ISM_{WD}) or ISM-WDSM (ISM_{WDSM}). The justification to add WD to denote a subcategory rather than a separate category is that the clinical course and prognosis are determined by the WHO-designated variant rather than the WD morphology of MCs. Nevertheless, in patients with a WD-subcategory of mastocytosis, unique laboratory and clinical features are detected, supporting the notion that the WD morphology should be reported. First, in most WD patients, no *KIT* D816V mutation is found. Rather other mutations in *KIT*, such as K509I or F522C, are detected (52, 56–58). As a result, some of these patients may respond to imatinib (60), which is not the case in patients who have *KIT* D816V+SM. Second, the phenotype of MCs in the WDSM group is different from that found in patients with *KIT* D816V. Notably, in most WD patients, MCs lack CD2 and CD25 (52, 56–59). However, MCs in WDSM often express CD30, which may be of diagnostic significance (59).

Potential value of CD30 as diagnostic criterion of systemic mastocytosis

Recent studies have shown that CD30, also known as Ki-1 antigen, is aberrantly expressed in the cytoplasm and on the surface of neoplastic MCs in systemic mastocytosis (59, 61, 62). However, CD30 is not expressed in MCs in all patients. In initial investigations, CD30 was found to be primarily expressed in MCs in advanced systemic mastocytosis (62). However, although a correlation does exist, CD30 is not an absolute marker of advanced systemic mastocytosis (ASM, MCL, SM-AHN), but is also detectable in MCs in many patients with ISM (59, 63). CD30 may thus not be an optimal grading marker in systemic mastocytosis, but may qualify as a new minor criterion of systemic

mastocytosis, similar to CD25. It is noteworthy in this regard that CD30 is usually detectable on MCs in patients with SM_{WDSM} (SM_{WD}; ref. 59). This is of importance as other minor systemic mastocytosis criteria may be absent in WD patients. Therefore, our consensus group recommends the inclusion of CD30 as a new minor systemic mastocytosis criterion in the future. In contrast, the value of CD2 as a minor systemic mastocytosis criterion is limited, which may support replacement of CD2 by CD30 as criterion. In fact, CD30 is a more sensitive parameter both in flow cytometry and IHC.

Refinements in B-Findings and C-Findings

Whereas B-Findings are generally indicative of a huge MC burden and involvement of multiple lineages in systemic mastocytosis, the presence of C-Findings is indicative of organ damage caused by the "invasive" MC infiltrate (20–22, 64). However, it is often difficult to define the relationship between systemic mastocytosis and organ damage or systemic mastocytosis and organomegaly, especially in cases with SM-AHN and patients with (other) comorbidities. In these patients, tissue biopsies may be necessary to document involvement by systemic mastocytosis and thus B- or C-Findings (65). Imaging techniques (e.g., volumetric techniques) may be helpful to quantify organomegaly (45). It has also been described that multicolor flow cytometry and cell sorting improves evaluation of lineage involvement in systemic mastocytosis (25, 46, 66) and that multilineage involvement in ISM/SSM is of prognostic significance (35, 46, 66). Moreover, it has been described that a certain *KIT* D816V allele burden in the peripheral blood (5%–10%) reflects multilineage involvement (30, 46). Therefore, we are of the opinion that (i) molecular studies revealing *KIT* D816V in various sorted leukocyte subsets and (ii) a *KIT* D816V allele burden of >5% in unfractionated peripheral blood leukocytes are robust indicators of multilineage involvement in systemic mastocytosis and should thus be nominated as potential new B-Findings. Whether these parameters will finally be accepted as novel B-Findings, and thereby can be used to predict or define the smoldering state in future classifications of mastocytosis, remains, at present, unknown.

Impact of somatic mutations in other genes (apart from *KIT*)

A number of recent studies have shown that in addition to activating mutations in *KIT*, additional mutations in other genes may occur in systemic mastocytosis (67–71). Most of these patients have SM-AHN, ASM, or MCL. In patients with SM-AHN, such additional lesions are often detectable in AHN cells. Mutations are commonly found in *TET2*, *SRSF2*, *ASXL1*, *CBL*, *RUNX1*, and *RAS* (Supplementary Table S4; refs. 67–72). Less common mutations include *JAK2* V617F and *RUNX1-RUNX1T1*. All these mutations may be coexpressed with *KIT* D816V in the same cells or may be expressed in other myeloid cells but not MCs, especially in SM-AHN. On the basis of colony assay studies, acquisition of *KIT* D816V may be a late event (71). Overall, the type and number of lesions (mutations) detectable in patients with multimitated systemic mastocytosis correlates with the clinical course and prognosis (72). Currently, the question remains whether additional molecular lesions detected in systemic mastocytosis can qualify as B-finding (2 or more B-Findings are required to diagnose SSM) or a criterion of an AHN. One reasonable approach may be to implement these mutations as a novel B-Finding provided that they do not lead to the diagnosis of an AHN. In other words, in

cases with additional criteria for an AHN, the same mutations should qualify as criteria of an AHN.

Delineation of MCL into subvariants

MCL was initially divided into the classical (leukemic) variant defined by at least 10% MCs (of all leukocytes) in the peripheral blood, and an aleukemic variant (<10% MCs in peripheral blood; refs. 20–23). However, MCL is a heterogeneous disease, both in terms of clinical presentation and survival (47). In some patients, MCL develops rapidly without a recognized prephase and with massive organ damage, whereas in other (rare) patients, there is a more chronic disease process without rapid organ damage. Therefore, MCL is now divided into an acute variant (with organ damage) and a chronic variant (without organ damage = without C-Findings), and also into primary MCL and secondary MCL (47). Secondary MCL variants have been described after a prephase of ASM or MCS. In general, all patients with MCL have a poor prognosis and should be treated with intensive therapy. However, in chronic MCL, treatment can be delayed (at least some weeks) whereas this is not advisable in acute MCL. An important differential in the diagnosis of MCL is myelomastocytic leukemia (MML; refs. 47, 73).

Therapeutic Options for Patients with Cutaneous Mastocytosis and ISM

A review of all treatment options in cutaneous mastocytosis and ISM is beyond the scope of this article. With regard to specific therapeutic algorithms, we refer to the available literature (1, 23, 31, 74, 75). In patients with mediator-related symptoms, HR blockers are recommended. In systemic mastocytosis cases with severe symptoms, additional pharmacologic agents such as corticosteroids, cromolyn sodium, ketotifen, or leukotriene antagonists may be applied. Some systemic mastocytosis patients with severe symptoms suffer from bee or wasp venom allergy. In these patients, specific immunotherapy should be administered lifelong to ensure protection. If immunotherapy is not effective, (additional) IgE-depleting treatment with omalizumab or similar experimental therapies should be considered. Another clinical challenge in systemic mastocytosis is osteoporosis. In all patients with systemic mastocytosis in whom the T score arrives at -2 , bisphosphonate therapy should be initiated (in the absence of contraindications). In drug-resistant cases, RANKL inhibitor therapy may be considered.

First-Line Therapy in Patients with Advanced Systemic Mastocytosis

First-line treatment of advanced systemic mastocytosis is a challenging problem. Before planning treatment, the following considerations should be taken into account: first, is the patient young and fit and in a transplantable condition? And, are there any relevant comorbidities that may interfere with transplant tolerability? Second, is the disease progressing rapidly or slowly? Third, what molecular targets are expressed by neoplastic cells? Finally, what organ systems are involved? In unusual cases (rare *KIT*-mutant forms or wild-type *KIT*) the disease may respond to imatinib (50, 51, 56, 57, 76). In a subgroup of ASM patients with slow progression, including those who present with isolated liver involvement (with recurrent ascites), low-dose prednisolone and IFN α may be efficacious (77–81). Cladribine (2CdA) is often

recommended as first-line therapy in patients with advanced systemic mastocytosis with multiorgan involvement and slow progression (82–85). A forthcoming new standard of therapy in advanced systemic mastocytosis is midostaurin (PKC412; refs. 86–88). For ASM/MCL patients with rapid progression and those who are resistant against 2CdA or midostaurin, poly-chemotherapy (protocols otherwise used for high-risk AML) is usually recommended (23, 64, 65). In patients who are young and fit and have a suitable donor, stem cell transplantation (SCT) should be considered after successful debulking. The outcome after allogeneic SCT is better in patients who have ASM or SM-AHN compared with MCL, and for those prepared with ablative conditioning compared with less-intensive (nonmyeloablative) conditioning (89). In patients with ASM-AHN, remission of the AHN is often achieved, whereas the ASM component of the disease cannot be eradicated (89). The overall response rate of ASM after SCT is similar when comparing ASM with ASM-AHN recipients. However, overall survival is better in patients with either ASM or ASM-AHN compared with patients with MCL (89). In those who relapse or are resistant, experimental drugs or alternative chemotherapies are recommended. For patients with SM-AHN, separate treatment plans for the systemic mastocytosis component and AHN component should be established; in such cases, the AHN should be treated as if no systemic mastocytosis was diagnosed, with recognition that any type of AHN counts as secondary: for example, in SM-AML, AML is regarded secondary and thus poor-risk AML.

New Treatment Options for Patients with Advanced Systemic Mastocytosis

During the past 15 years, a number of novel treatment concepts for MC-proliferative disorders have been established. As mutant forms of *KIT*, especially *KIT* D816V, are critically involved in the pathogenesis of systemic mastocytosis, attempts have been made to develop drugs that are directed against this target receptor. The most well-known example is midostaurin, a drug that inhibits the growth of neoplastic MCs exhibiting various mutant forms of *KIT*, including *KIT* D816V (90, 91). In addition, in contrast to other *KIT*-targeting drugs, midostaurin also inhibits IgE-dependent release of histamine (92, 93). Finally, midostaurin has been reported to be efficacious in patients with advanced systemic mastocytosis, including ASM and MCL (86–88). In particular, data from the global trial of midostaurin in advanced systemic mastocytosis indicate that the drug exhibits high response rates and durable activity (86). These data are the basis of the current submission to the health authorities, and if the drug is approved for advanced systemic mastocytosis, midostaurin can be regarded as standard first-line therapy of patients with advanced systemic mastocytosis. The drug may also be useful for patients who need debulking prior to SCT or those who fail treatment with 2CdA or IFN α . However, midostaurin does not induce complete hematologic remissions in patients with advanced systemic mastocytosis. Therefore, future studies should consider evaluating the benefit of combining midostaurin with other drugs. Indeed, midostaurin and 2CdA exert strong synergistic antineoplastic *in vitro* effects on MCs carrying *KIT* D816V (90). It is also noteworthy that *KIT* D816V *per se* is not considered to act as a strong oncoprotein but rather as a differentiation-inducer in neoplastic cells (94), an assumption that is supported by the observation that *KIT* D816V is expressed in patients with ISM where life expectancy

is normal (19–23, 34). Therefore, the current view is that additional, KIT-independent pathways and pro-oncogenic hits and lesions are responsible for disease progression and resistance (67–72), which is supported by the observation that relapsing disease in KIT D816V+ SM during midostaurin may present as KIT D816V–negative leukemia (95). On the basis of these observations, it seems reasonable to suggest that additional pathways and effector molecules need to be blocked to achieve disease eradication. Such target pathways and molecules include, among others, RAS, PI3K, mTOR, STAT5, and members of the BCL-2 family. Some of these molecules are expressed (and activated) in neoplastic MCs in both a KIT-dependent and KIT-independent manner. It has also been shown that suppression of these targets is associated with growth inhibition and apoptosis of neoplastic MCs (96–98). However, these effects may be largely restricted to proliferating cells, whereas nonproliferating neoplastic stem cells are often resistant. Such MCL-initiating stem cells have recently been identified in advanced systemic mastocytosis (98). One effective approach to kill such quiescent (stem) cells may be to apply antibody-based toxin conjugates or other targeted antibodies (63, 99, 100). The CD30 antibody-based drug brentuximab vedotin has recently been considered for the treatment of patients with advanced systemic mastocytosis (63), and a clinical trial in patients with CD30⁺ ASM and MCL has recently been initiated in the United States.

Concluding Remarks and Future Perspectives

Mastocytosis is a paradigmatic example of a rare disease with complex pathology, distinct subtypes, and highly variable clinical courses, ranging from asymptomatic with normal life expectancy to fatal within months or weeks. The management of these disorders requires a deep understanding of their molecular and cellular pathogenesis and a precise diagnostic evaluation. Unfortunately, mastocytosis remains incurable, and in those with advanced systemic mastocytosis, the prognosis is still dismal. In other cases, the prognosis is good regarding survival, but mediator- and symptom burden can be considerable and the quality of

life may be poor. However, in the past few years, novel treatment approaches have been developed. Most promising drugs are those that target mutant forms of KIT and other critical target molecules. For patients with advanced systemic mastocytosis who are young and fit and have a suitable donor, allogeneic SCT is a realistic option and can be recommended in drug-refractory disease.

Disclosure of Potential Conflicts of Interest

P. Valent reports receiving a commercial research grant from Deciphera, has received speakers bureau honoraria from Novartis, and is a consultant/advisory board member for Novartis and Deciphera. C. Akin has provided expert testimony for Novartis, Deciphera, and Blueprint. K. Hartmann reports receiving a commercial research grant from Novartis, has received speakers bureau honoraria from Novartis, ALK, and AbbVie, and is a consultant/advisory board member for Novartis and Deciphera. A. Reiter has received speakers bureau honoraria from Novartis Pharma and Deciphera and is a consultant/advisory board member for Novartis Pharma. O. Hermine reports receiving a commercial research grant from Novartis, AB Science, Lipomed, has ownership interest (including patents) in AB Science, and is a consultant/advisory board member for AB Science. W.R. Sperr reports receiving a commercial research grant from Phadia and has received speakers bureau honoraria from Phadia. T.I. George reports receiving a commercial research grant from Allakos and is a consultant/advisory board member for Novartis and Blueprint. J. Gotlib reports receiving other commercial research support from Novartis, Blueprint Medicines, Seattle Genetics, and Pharmacyclics and is a consultant/advisory board member for Novartis and Deciphera. L.B. Schwartz reports receiving a commercial research grant from Novartis (midostaurin clinical trial), has ownership interest (including patents) in Thermo Fisher (tryptase immunoassay), and is a consultant/advisory board member for Deciphera. No potential conflicts of interest were disclosed by the other authors.

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