REVIEW ARTICLE

blood advances

Systemic mastocytosis: current status and challenges in 2024

Celalettin Ustun,[1] Fatma Keklik Karadag,[2] Michael A. Linden,[3] Peter Valent,[4,5] and Cem Akin[6]

[1]Division of Hematology, Oncology and Cellular Therapy, Department of Medicine, Rush University Medical Center, Chicago, IL; [2]Division of Hematology, Izmir City Hospital, Izmir, Turkey; [3]Division of Hematopathology, Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN; [4]Division of Hematology and Hemostaseology, Department of Internal Medicine and [5]Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Vienna, Austria; and [6]Division of Allergy and Clinical Immunology, University of Michigan, Ann Arbor, MI

Systemic mastocytosis (SM) is a rare disease and has had significant discoveries in its biology, prognostication, and management in the past 2 decades. The latest update of the World Health Organization classification and the new International Consensus Classification are current standards in the diagnosis and prognostication of SM. In clinical practice, SM can be divided into 2 main categories: nonadvanced SM (nonAdvSM) and advanced SM (AdvSM). The integration of clinical signs and symptoms as well as bone marrow morphologic, immunophenotypic, and molecular results is required to diagnose SM variants. In the modern era, data with KIT inhibitors (ie, avapritinib) suggest prolongation of survival in AdvSM. Although this is encouraging progress, and we now have effective drugs for managing both patients with indolent SM and AdvSM, there are remaining challenges in SM. For example, optimal initial treatment in certain patient subsets, such as SM with an associated hematologic neoplasm (SM-AHN), remains under debate (eg, treatments targeting AHN or SM, monotherapy, or combinations). Prospective studies evaluating drugs with different mechanisms of action are needed for such patients. This review provides an updated overview of SM, including the latest methods for diagnosis, patient classification based on their prognosis, and management according to the most significant clinical trials, covering both patients with nonadvSM and AdvSM.

Introduction

Mastocytosis is a rare disease characterized by a substantial increase and accumulation of clonal mast cells (MCs) in the skin only (cutaneous mastocytosis) or in various extracutaneous organs (systemic mastocytosis [SM]) with or without skin involvement.[1-3] SM can be categorized into 2 main clinical groups[4-12]: nonadvanced SM (nonAdvSM) and advanced SM (AdvSM). NonAdvSM includes indolent SM (ISM), bone marrow mastocytosis (BMM), and smoldering SM (SSM) whereas AdvSM includes SM with an associated hematologic neoplasm (SM-AHN), aggressive SM (ASM), and MC leukemia (MCL) (Figure 1). The International Consensus Classification (ICC) uses the term SM–associated with myeloid disease instead of SM-AHN because most AHN cases are myeloid neoplasms.

Symptoms and signs of SM result from tissue damage caused by infiltration of tissues or organs by neoplastic MCs or the activation of neoplastic MCs, leading to the release of MC mediators.[1-4,9-11,13,14] Patients with nonAdvSM have a normal or near-normal life expectancy, whereas patients with AdvSM

Submitted 1 May 2024; accepted 8 January 2025; prepublished online on *Blood Advances* First Edition 24 January 2025; final version published online 23 April 2025. https://doi.org/10.1182/bloodadvances.2024012612.

Figure 1. Classification and clinical features of SM according to revised WHO classification (fifth edition) in 2022 and ICC. [a]These findings are defined as B-findings. [b]These findings are defined as C-findings. #Bone marrow dysfunction manifested by ≥1 cytopenias (absolute neutrophil count of <1 × 10^9/L, hemoglobin [Hb] of <10 g/dL, platelets of <100 × 10^9/L but no obvious non-MC hematopoietic malignancy. ##Liver dysfunction with ascites, and/or portal hypertension. ###Large osteolytic lesions and/or pathologic fractures. Of note, ICC includes BMM in ISM and uses associated myeloid neoplasm (AMN) instead of AHN in the subset of SM-AHN. Also, by ICC, a core biopsy specimen may be used to diagnose MCL if the aspirate is a "dry tap."

have significantly reduced survival rates compared with both patients with nonAdvSM and healthy controls.[15-18] Therefore, a precise subclassification is essential for management and prognostication.

Diagnosis and classification

The diagnosis of SM is well defined based on the major and minor SM criteria outlined in Table 1.[4,9-14] The fifth edition of the World Health Organization (WHO)[11] and the ICC[19] have very similar diagnostic categories with some differences. The WHO requires 1 minor criterion if the major criterion is present, whereas the ICC allows a diagnosis of SM with only the major criterion.[20] The new EU/US consensus group, WHO, and ICC classifications feature several major elements: tryptase and/or CD117 immunoreactivity must confirm the multifocal dense MC aggregates, CD30 is a new minor SM criterion, especially in well-differentiated MCs and in well-differentiated SM, and all activating *KIT* mutations are accepted as minor SM criteria.[11,21] The WHO requires >20% MCs in the BM aspirate for diagnosis of MCL, which may be a problem in patients with unsuccessful "dry tap" BM aspirates. The new EU/US, WHO, and ICC proposals have also introduced subtle changes.[20] Although the WHO may miss a few real patients with patients with SM due to the lack of minor criteria, it is unlikely that all minor criteria will be falsely negative in a single patient. ICC-based SM diagnosis may incorrectly identify patients with MC hyperplasia, *PDGFR*-mutated myeloproliferative neoplasms (MPNs), or myelomonocytic leukemia as having SM. However, WHO and ICC diagnoses are expected to match in most patients.

Table 1. Diagnostic criteria of SM

Major criterion	Minor criteria
Multifocal dense infiltrates of MCs (>15 MCs in aggregates) in BM biopsies and/or in sections of other extracutaneous organ(s)*	1. In BM biopsy or in sections of other extracutaneous organs >25% of MCs are spindle shaped or have an atypical immature morphology 2. MCs in the BM, PB, or other extracutaneous organs express CD25, CD2, and/or CD30†, in addition to MC markers 3. *KIT* D816V mutation or other activating *KIT* mutation detected in the BM, PB, or other extracutaneous organs‡ 4. Elevated serum tryptase level, persistently >20 ng/mL†,§

For the diagnosis of SM, 1 major + 1 minor or >3 minor criteria needed for WHO, and 1 major or >3 minor criteria needed for ICC classification.

AMN, associated with myeloid disease.

*Tryptase and/or $CD117^+$ MCs.

†According to ICC, aberrant CD30 expression on the MCs has been added as an additional immunophenotypic finding.

‡According to ICC, to avoid false-negative results, use of a high sensitivity PCR assay for detection of *KIT* D816V mutation is recommended. If negative, exclusion of KIT mutation variants is strongly recommended in suspected SM.

§For patients with SM-AMN, an elevated tryptase does not count as a SM minor criterion. If the patient has hereditary α-tryptasemia, the tryptase level should be adjusted.

Despite these advances, the diagnosis of a patient may be challenging and could take months to years to arrive at a correct diagnosis.

In whom should SM be considered?. Patients with SM may have various symptoms and signs affecting multiple organ systems, although these may be nonspecific. Common allergic/hypersensitivity reactions are triggered by mediators derived from MCs such as histamine, heparin, leukotrienes, prostaglandins, platelet-activating factor, proteases, and cytokines (eg, tumor necrosis factor [TNF]).[1,2] Skin symptoms such as itching and flushing are prevalent. Maculopapular mastocytosis lesions, present in ~80% of patients, may urticate with friction or irritation. Gastrointestinal tract (GIT) symptoms (abdominal pain, cramps, distention, constipation, and diarrhea) are common in up to 80% of patients. Weight loss is more common in advanced mastocytosis (AdvSM) than in non-AdvSM. Fatigue is a common nonspecific symptom, whereas fever is rare, except in cases of AHN or very aggressive AdvSM/MCL. Neurologic symptoms include headaches, migraines, and cognitive dysfunction (brain fog). Neuropsychiatric manifestations, such as depression, mood changes, lack of concentration, short memory span, increased somnolence, irritability, high anxiety levels, and emotional instability, are common in adult patients with SM, particularly those with nonAdvSM.[22] Musculoskeletal pain without a clear evidence of inflammation is common, although its association with SM is unclear because of varying responses to SM-directed therapy. Osteopenia or osteoporosis, even in asymptomatic patients, is detected in both nonAdvSM and AdvSM. Hypotension and syncope are more common in patients with a concomitant allergy.

Signs. Typical skin lesions, if present, can be very useful for diagnosing SM, but they are less common in adults, especially those with AdvSM. These lesions are named maculopapular cutaneous mastocytosis, formerly urticaria pigmentosa (Figure 2). However, skin lesions do not determine the mastocytosis category; most patients with SM have maculopapular cutaneous mastocytosis lesions. Some patients with SM have BMM or AdvSM, including many with MCL.

Hepatosplenomegaly due to abnormal MC accumulation can be apparent on physical examination in SSM and AdvSM. Splenomegaly, with or without hepatomegaly, and enlarged lymph nodes are common in patients with SM (can be a B-finding).[23] Ultrasonography and computed tomography (CT) are preferred for evaluating the liver, spleen, lymph nodes, and mass lesions.[6,7] Elastograms, performed using ultrasound or magnetic resonance imaging, assess fibrosis associated with MC infiltration. Ascites are common, whereas liver cirrhosis with variceal bleeding is rare in AdvSM.[24,25] GIT endoscopies and biopsies show mucosal involvement.[26] Duodenal or gastric ulcers and severe duodenitis can occur.[27-29] Malabsorption, characterized by weight loss and hypoalbuminemia, can result from MC infiltrations of villous structures.[26,30] Imaging underestimates GIT involvement. The colon wall thickening is the most significant radiological finding; enlarged mesenteric lymph nodes, and dilatation and/or widespread mucosal nodular-polypoid lesions can also be seen.[31,32]

Figure 2. Urticaria pigmentosa in a patient with SSM. Informed consent and written permission were obtained from the patient.

Osteopenia and osteoporosis are common and should concern SM, especially young, otherwise healthy patients. Both sexes are affected. In SM, lytic bone lesions and osteosclerosis may occur in the axial and appendicular skeleton, but larger regions of osteolysis with bone fractures (a "C-finding") are rare and typically seen in patients with AdvSM.[33,34] Bone scintigraphy, radiography, and densitometry characterize skeletal involvement and assess disease severity.[31] Densitometry is crucial for assessing bone dynamics and treatment responses in osteopenia and osteoporosis.[31,34] SM-related osteopathy is caused by direct and indirect effects of MCs, including the release of mediators such as TNF, interleukin-6, Receptor activator of nuclear factor kappa-B ligand (RANKL), prostaglandins, histamine, heparin, proteases, and MC accumulation.[31]

Peripheral blood (PB) and BM evaluations are critical for evidence of morphologic qualitative (dysplasia or fibrosis) or quantitative (cell counts, blast counts, or cellularity) abnormalities. BM aspirate/biopsy must undergo flow cytometry (FC), cytogenetic studies, and immunohistochemistry (IHC). Elevated serum alkaline phosphatase (ALP) activity, particularly in advanced SM, is a common but nonspecific abnormality and a prognostic factor.[18,35] A recent study found a correlation between elevated serum ALP levels and a high MC burden in liver tissue.[25]

The role of positron-emission tomography/CT in SM is unclear; however, it is limited in SSM and ASM, as shown in a multicenter French study.[36] In SM-AHN and ASM, increased [^{18}F]fluorodeoxyglucose uptake is expected in cortical bone, the BM, and various organs because of MC infiltration.[37,38]

How to diagnose SM?. A multidisciplinary approach, including symptom review and clinical examination, is essential for patients with suspected SM.[39,40] Basal serum tryptase levels can be used as a screening test; >20 ng/mL can be detected in >70% of patients with SM (Figure 3).[23] In these patients, a *KIT* D816V mutation increases the likelihood of SM. A BM biopsy is recommended for all patients with suspected SM. Although tryptase screening is simple, not all patients have elevated levels, and ICC does not require a minor criterion for SM diagnosis with the major criterion. Mean tryptase levels vary, but markedly increased levels (>200 ng/mL) are more common in SSM, ASM, MCL, and SM-AHN.[15] Tryptase levels are lower in nonAdvSM (except SSM) than in AdvSM, but there is no absolute correlation between MC burden, tryptase levels, symptoms, or disease aggressiveness/prognosis. Patients with BMM with low tryptase often have severe

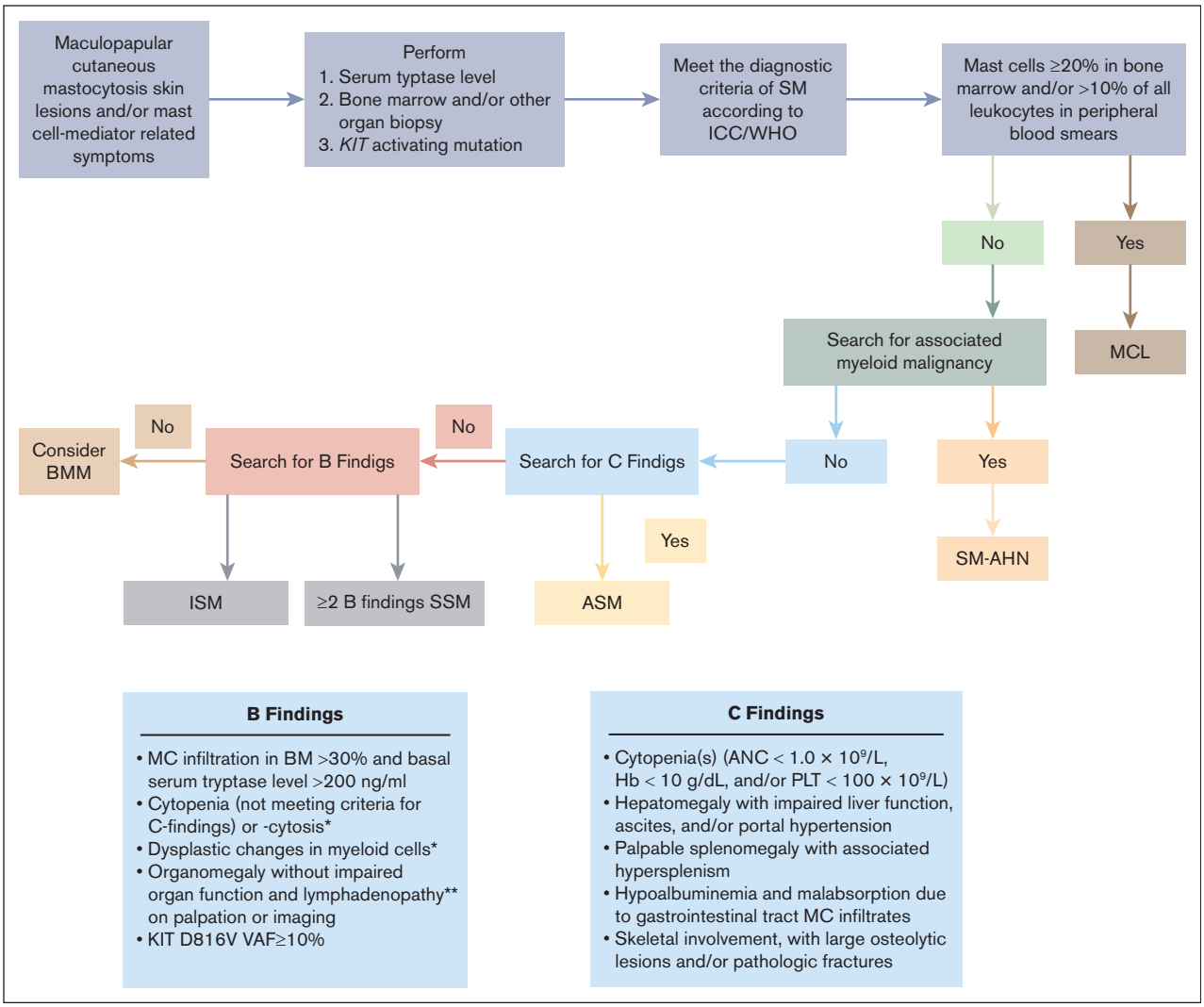

Figure 3. Diagnostic algorithm of SM. *Reactive causes are excluded, and criteria for other myeloid neoplasms are not met. **Lymphadenopathy as a B-finding is defined as >1 cm and 2 cm according to ICC and fifth edition of the WHO classification, respectively. ANC, absolute neutrophil count; PLT, platelet.

symptoms, whereas patients with SM with higher tryptase levels may have milder symptoms. Elevated tryptase in the general population is usually due to a higher copy number in the *TPSAB1* gene encoding α-tryptase (hereditary-α-tryptasemia, HaT), which is seen in up to 7% of the population, most of whom are asymptomatic. SM and HaT are not mutually exclusive; several studies have shown a higher prevalence of HaT in SM.[41] Patients with concurrent SM and HaT may experience more severe MC activation and anaphylaxis.[41] Serum tryptase reference ranges should be adjusted for patients with SM and HaT, but a consensus on the optimal correction method is lacking.[11] Elevated basal serum tryptase levels can also be observed in MPN or myelodysplastic syndrome (MDS), renal failure, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), and chronic eosinophilic leukemia.[42] Some endocrine tumors, such as carcinoid syndrome, Zollinger-Ellison syndrome, medullary thyroid cancer, and pheochromocytoma, can cause paroxysmal episodes of flushing and diarrhea similar to SM, but serum tryptase levels are not elevated in these conditions.

BM examination is the recommended diagnostic procedure for diagnosing SM (Figure 4). It is essential for classifying SM and recognizing and classifying AHN. IHC staining of BM cells for MC tryptase (MCT), CD117/KIT, CD2, CD25, and CD30 should be performed.[43-46] Tryptase (MCT) and CD117 are sensitive markers for recognizing MCs, but neither distinguishes abnormal MCs from normal MCs. Both CD117 and MCT tests are important, because MC neoplasms may degranulate, resulting in weak or absent MCT staining but strong CD117 staining. FC underestimates the MC burden and can be falsely negative in BM aspirates because MCs stick to bony trabeculae. CD117 vs side scatter plots in FC can detect abnormal MCs that have bright CD117, high side scatter, and form a discrete population (Figure 5).[47] If present, then CD2 and/or CD25 expression should be tested in these cells. CD25 and/or CD2 and/or CD30 expression on BM MCs defines abnormal MCs and supports the diagnosis of SM.[46] If performed concurrently, CD2 and CD25 on MCs may be more sensitive markers by FC than by IHC staining.[48] CD25 is usually positive on abnormal, spindle-shaped neoplastic MCs and is more sensitive

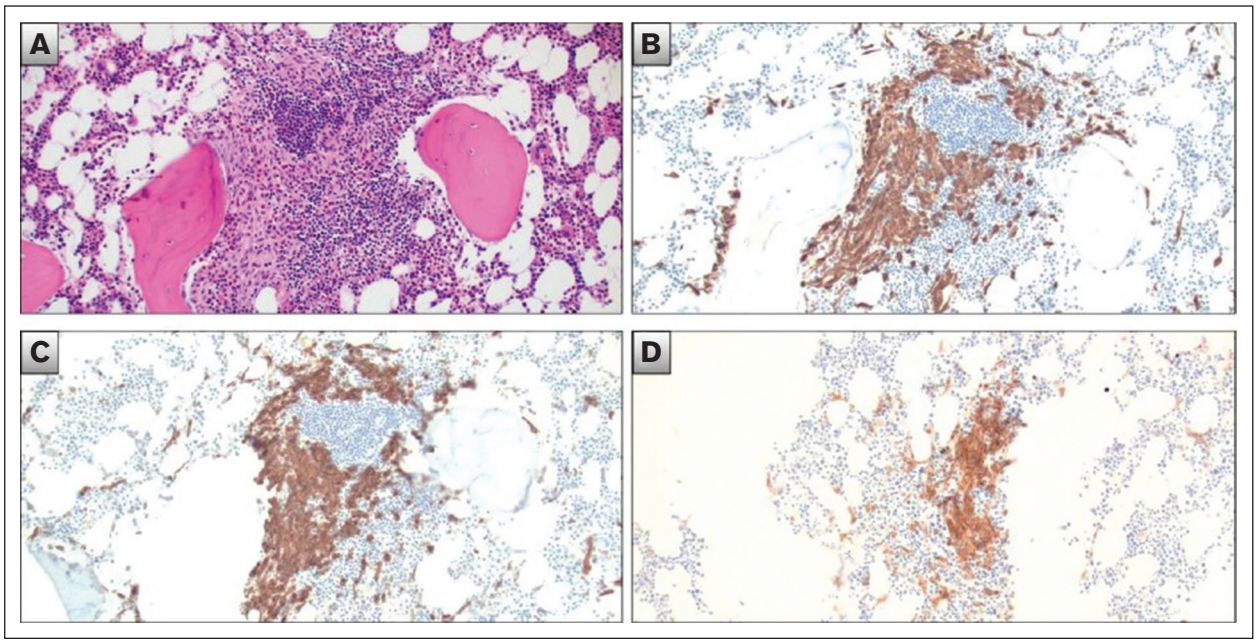

Figure 4. Bone marrow findings in SM. All images captured using a ×20 objective. (A) Hematoxylin and eosin–stained section of a BM core shows an atypical, partially paratrabecular MC aggregate composed of numerous spindle-shaped MCs. There is a reactive lymphoid aggregate present adjacent to the MC aggregate (confirmed by IHC [not shown] and concurrent negative flow cytometry for B and T cells). The MCs uniformly express strong CD117 (B) and MC tryptase (C). The MCs also aberrantly express CD25 (D) but lack CD2 or CD30 expression (not shown). Morphology and flow cytometry also excludes a myeloid neoplasm. Although a flow study was attempted to analyze the MCs, the patient's involvement was patchy; there were too few MCs on the flow study to interpret CD2 and CD25 expression.

than CD2[49] (Figure 5). Round MCs in well-differentiated SM are more likely to express CD30 but lack CD2 and CD25.[21] Both the ICC and WHO fifth edition recommendations have incorporated CD30 expression. Aberrant CD30 positivity on MCs is specific to all forms of SM but has only a weak prognostic value.[11,49-51]

In patients with SM-AHN, sheets of neoplastic AHN cells (eg, AML and CMML) may obscure/mask the SM. These AHNs are more common in clinical practice and may lead to overlooking the diagnosis of coexisting SM (occult SM in SM-AHN).[52,53] If there is a clinical suspicion (allergy, high serum tryptase) and/or next-generation sequencing (NGS) shows a *KIT* mutation, reevaluating the BMs (typically ordered for the AHN) can correctly diagnose SM-AHN. Occult SM can be diagnosed easier, evaluating BM biopsy samples later in treatment when the obscuring cells are cleared and the abnormal MCs, resistant to treatment, persist.[54,55]

Careful morphologic evaluation of the GIT mucosa hematoxylin and eosin–stained sections is important; however, using IHC stains for MCT and CD117 to identify dense clusters/bands of MCs rather

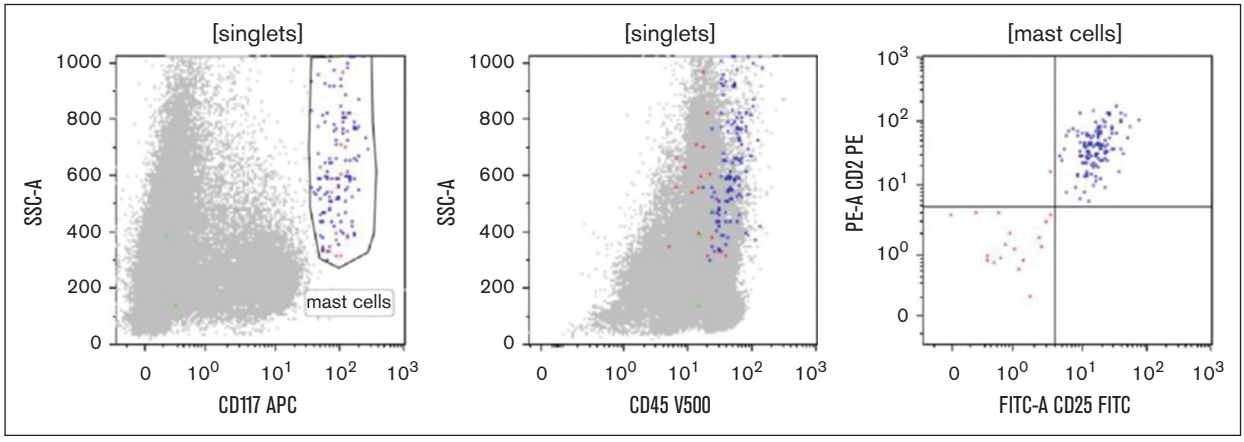

Figure 5. Flow cytometry findings in SM. Viable singlets are analyzed, and MCs are identified based on their bright surface CD117 expression and high SSC (right angle light scatter that increases in cells with cytoplasmic granules, such as in MCs), left-most plot. Typically, in SM, as in this case, there is a "discrete" MC population based on CD117 vs SSC. The middle plot shows the MCs fall on CD45 vs SSC, falling in an area between in which neutrophils and eosinophils typically fall. The right-most plot shows the aberrant expression of CD2 and CD25 by the MCs (color gated in blue), and the red dots likely correspond to a few residual normal MCs. APC, antigen-presenting cell; FITC, fluorescein isothiocyanate; PE, phycoerythrin; SSC, side scatter.

than the absolute number of MCs in a high-power microscopic field may be helpful. If clusters are present, assessing for aberrant expression of CD2, CD25, and/or CD30 is recommended. Multiple biopsies are usually necessary because of focal and moderate GIT infiltration.

KIT is a receptor tyrosine kinase on MCs. More than 90% of patients with SM have a somatic point mutation of exon 17 in the *KIT* gene, typically in the codon 816, which substitutes valine for aspartate (Asp816Val).[56] Although the D816V mutation is the most common, V560G, D815K, D816Y, and other mutations have been identified in <5% of patients with SM.[57] In a significant proportion of patients with well-differentiated SM (90%), MCL (20%-30%), or ASM (5%), other mutations in *KIT* or no *KIT* mutations are detected. Pediatric patients are also more likely to carry other *KIT* mutations, including mutations in exon 8. NGS can be a screening test to detect a *KIT* mutation for SM-AHN. In most cases, *KIT* D816V is detected even in morphologically-occult SM, as mentioned earlier. In contrast, in cases in which a morphologic examination of the BM biopsy positive for SM, but standard NGS is negative for a *KIT* mutation, sensitive polymerase chain reaction (PCR) tests such as droplet digital PCR or allele-specific PCR for variants with an allele frequency (VAF) of <0.1% should be performed. This is essential to avoid adverse consequences because some KIT inhibitors (imatinib) are ineffective in *KIT* D816V-mutated SM. *KIT* can be tested in the PB and myeloid AHN cells (monocytes in SM-CMML, 89%; myeloid progenitors in SM-MPN, 20%; and blasts in SM-AML, 30%) in patients with SM-AHN.[58] This multilineage involvement is typically found in SM-AHN but can also be seen in other types of SM and is known to be an independent poor prognostic factor for ISM.[59]

Mutations in *SRSF2*, *ASXL1*, *RUNX1*, *JAK2*, *NRAS*, and *TET2*, although not specific to SM, have been detected in SM.[60-62] These mutations are more likely to be found in SM-AHN and can also be rarely detected in patients with nonAdvSM, serving as important prognostic factors.[63]

What is next after making a diagnosis of SM?. After having made the diagnosis of SM, it is crucial to identify the specific subset for the patient, because the prognosis varies significantly.[4,10,11] BMM, ISM, and SSM, which have increasing MC burden in this order, are the nonaggressive forms of SM and lack a "C-finding."[10,11,13,64] SSM requires a "B-finding" that indicates an increased MC burden (BM MCs of ≥30%, tryptase of >200 ng/mL, and *KIT* D816V VAF of ≥10% by WHO, but not by ICC)[13] or evidence of myeloproliferation and/or myelodysplasia (not meeting WHO criteria for a specific clonal myeloid neoplasm). It is important to distinguish between B-findings and C-findings (SM-induced organ damage) in all patients. For instance, hepatosplenomegaly alone is not considered a C-finding, but severe hypersplenism, liver dysfunction with ascites, or severe cytopenia are, if the organ damage is caused by local MC infiltrates.

ASM diagnosis requires at least 1 C-finding for organ damage from high MC burden and exclusion of MCL defined as >20% MCs, usually immature, in the BM aspirate (Figure 3).[8,13] SM-AHN, the second most common SM type, requires both SM and hematologic malignancy criteria. The SM component in SM-AHN can be advanced or nonadvanced. The AHN is almost always myeloid, as with MDS, MPN, or MDS/MPNs. In patients who are eosinophilic, tyrosine kinase gene fusions associated with myeloid/lymphoid neoplasms with eosinophilia and kinase gene fusion (M/LN-eo) must be excluded if a *KIT* mutation is not detected. However, rare cases of true SM with an associated eosinophil neoplasm occur, and both relevant *KIT* mutations and *PDGFR* rearrangements may be detected.

SM is a spectrum of disease from indolent to advanced forms (Figure 6). It is similar to plasma cell dyscrasias, ranging from monoclonal gammopathy of unknown significance to smoldering and multiple myeloma. Placing a patient within this spectrum is crucial for prognosis and management. Over time, some progression will likely occur in most of these patients, but for many, it may not have significant clinical implications during their lifetime (eg, chronic lymphocytic leukemia). ISM (3%-5%) and SSM (9.4%) can rarely progress to advanced forms.[65] Using prognostic factors, one can locate the clinical phase of a patient with nonAdvSM more accurately. Some scoring systems, such as the International Prognostic Scoring System, are available and validated.[16-18,35] Age (≥60 years) and higher serum ALP (≥100 U/L) are independent prognostic variables for overall survival (OS) in nonAdvSM

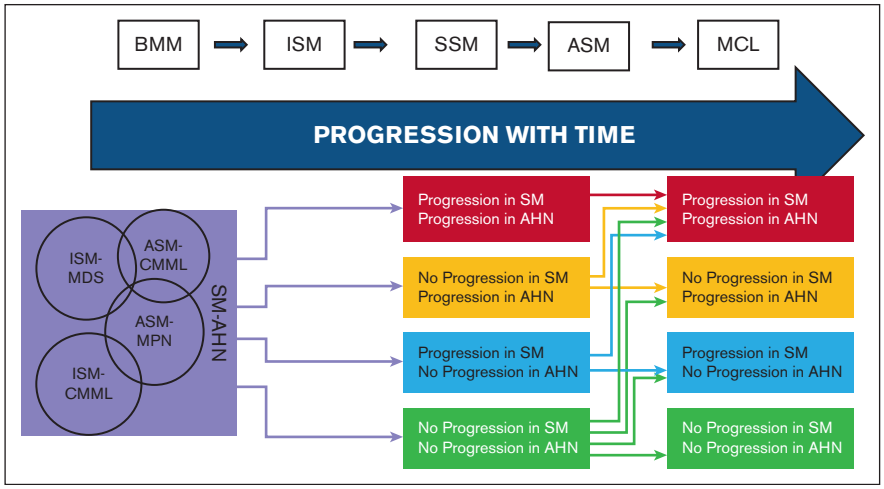

Figure 6. Progression timeline from NonAdvSM to AdvSM seems to follow a straight line for SM. However, in SM-AHN, the progression of AHN, SM, or both over time is less predictable because of heterogeneity and limited knowledge of risk factors.

(n = 1380).[16] The 10-year OS was 98%, 87%, and 52% for patients with no, 1, and 2 risk factors, respectively. OS and progression-free survival (PFS) varied across these risk groups; rates of 96%, 87%, and 61% for OS and PFS, respectively, were found. In a recent European registry study, some other serum chemistry markers (lactate dehydrogenase, albumin, β-2-microglobulin, vitamin B_{12} level, and C-reactive protein) were found as prognostic factors.[66] Higher TNFα levels were associated with treatment resistance and poor survival.[67] Some studies have incorporated genetic aberrations and mutations (eg, *SRSF2*, *ASXL1*, and/or *RUNX1*) into the scoring systems.[17,68] In a recent study, high levels of KIT VAF (≥6%) were detected in 15% of patients (37/246) enrolled in the PIONEER study (avapritinib in nonAdvSM).[69] Compared with patients with a lower VAF of *KIT* mutation, these patients were older, had a longer history of SM, a higher tryptase, a higher proportion of BM MCs, and a lower rate of anaphylaxis. OS was lower in patients with a higher VAF, both in the low International Prognostic Scoring system score group (41% vs 65%) and the intermediate 1 to 2 group (59% vs 35%).

Treatment

Until recently, cytoreductive treatments such as interferon-α2b, hydroxyurea, and cladribine (2-chlorodexoyadenosine) were used in AdvSM, but rarely used, off-label, for patients with nonAdvSM with severe symptoms such as recurrent anaphylaxis or severe skeletal involvement (Table 2). Symptom control in most ISM has been achieved with receptor blockers, MC stabilizers, and a monoclonal anti–immunoglobulin E antibody, and omalizumab.[70] Recently, potent inhibitors of MC activation and expansion have been developed and tested in clinical trials, including KIT inhibitors (dasatinib,[71] imatinib,[72] and masitinib[73]). Imatinib was approved by the US Food and Drug Administration for SM with *KIT* WT. Strong inhibitors of *KIT* D816V, such as midostaurin and avapritinib,[74,75,76,77,78] suppress MC expansion by inducing cell death in MCs and their progenitors. The toxicity profiles of these drugs were generally acceptable.[74,76] Both drugs also showed beneficial effects on MC mediator–induced symptoms, resulting in a reduction of overall symptom scores and increased quality of life (QOL).[78,79] The rapid effects of midostaurin and avapritinib on

Table 2. A summary of some of the studies evaluated the cytoreductive therapies in AdvSM

Drug	Number of patients	Overall response rate	Median follow-up, mo (range)	Median duration of response, mo (range)	OS and PFS	Adverse events
Cladribine[86]	68 ISM = 36 AdvSM = 32	92% ISM 50% AdvSM	69.6 (0.7- 108)	44.4 (1.2-13.2)	OS, 48.5% (95% CI, 30.2-77.9) PFS, 23.4% (95% CI, 10.7-51.2)	Grade 3-4; lymphopenia, neutropenia, and opportunistic infections
Interferon-α with or without prednisolone[87]	47 ISM = 11 ASM = 14 SM-AHN = 22	60% ASM 45% SM-AHN		12 (1-67)	NA	Common: fatigue, depression, and thrombocytopenia
Midostaurin[74]	116 ASM = 16 SM-AHN = 57 MCL = 16	75% ASM 58% SM-AHN	26 (12-54)	24.1 (95% CI, 10.8 to not estimated)	Median OS, 28.7 mo (95% CI, 20.3-45.5) Median PFS, 14.1 mo	Common: nausea, vomiting, diarrhea, and cytopenia Grade 3-4: fatigue, nausea, vomiting, diarrhea, and cytopenia
Midostaurin[88]	26 ASM = 3 SM-AHN = 17 MCL = 6	69%	124 (82-140)	Not reached at 37.8	Median OS, 40 mo (95% CI, 1.2-134.6 mo) Median PFS was 41.0 mo (95% CI, 4.4-77.6)	Common: nausea, vomiting, constipation, fatigue, lower extremity edema, headache, and diarrhea Grade 3-4: asymptomatic hyperlipasemia, dyspnea, elevated ALP, and cytopenia
Midostaurin[89]	33 ASM = 17 SM-AHN = 14 MCL = 2	53% ASM 29% SM-AHN 50% MCL	14.6	21.5 (2.9-123)	Median OS, 19.3 mo	Common: GI toxicity and cytopenia Grade 3-4: neutropenia and thrombocytopenia
Avapritinib[75] Phase 2 PATHFINDER trial	62 ASM = 9 SM-AHN = 43 MCL = 10	75%	23	NA	The estimated OS at 1 year 86% PFS at 1 year 79%	Common: peripheral-periorbital edema, diarrhea, nausea, vomiting, cytopenia, and cognitive effects Grade 3-4: cytopenia, peripheral-periorbital edema, diarrhea, nausea, and vomiting
Avapritinib[76] Phase 1 EXPLORER trial	69 ASM = 8 SM-AHN = 48 MCL = 13	75%	23	38 (95% CI, 22 to not estimable)	Median OS was not reached The estimated PFS at 1 year 84%	Common: periorbital edema, cytopenia, diarrhea, intracranial bleeding, and cognitive effects Grade 3-4: cytopenia, fatigue, cognitive effect, nausea, and intracranial bleeding
AlloHCT[90]	57 ASM = 7 SM-AHN = 38 MCL = 12	70%	32 (3- 202)	20	OS at 1 year 62% PFS at 1 year 57%	NRM at 1 year, 20%
AlloHCT[91]	71 AdvSM = 58 MCL = 13	NA	16.8 (0-244.8)	NA	OS at 1 year 62% PFS at 1 year 52%	NRM at 1 year, 23%

CI, confidence interval; NA, not available; NRM, nonrelapsed mortality.

mediator-related symptoms and QOL may be because of their direct inhibitory effects on MC activation and basophil activation.[77,80] In a retrospective study, avapritinib prolonged survival in adults with AdvSM compared with prior therapies.[81] The 3-year follow-up responses were durable.[82] In May 2023, the US Food and Drug Administration has approved both midostaurin and avapritinib for the treatment of AdvSM, and avapritinib for adults with ISM (Table 2). Avapritinib is not recommended for the patients with AdvSM with platelets of $<50 \times 10^9$/L. Midostaurin is a multikinase inhibitor that inhibits both WT and *KIT* D816V, whereas avapritinib selectively inhibits *KIT* D816V. Avapritinib was approved for second-line therapy in AdvSM by the European Medicines Agency. Bezuclastinib, an investigational tyrosine kinase inhibitor (TKI) with D816V *KIT* selective inhibition, decreased BM MC burden, serum tryptase, and *KIT* mutant allele fraction. This treatment was well tolerated and showed promising clinical activity in both AdvSM and nonAdvSM; data await peer review.[83,84] Elenestinib, a novel, oral, next-generation D816V *KIT* selective TKI, showed promising results in a large cohort of patients with ISM with moderate-to-severe symptom burden.[85]

Allogeneic hematopoietic stem cell transplantation (allo-HCT) is the only known potentially curative treatment option for AdvSM (Table 2).[90] Allo-HCT is regaining importance because of the development of effective KIT inhibitors, which enable better control of AdvSM and thereby allow patients with advSM to survive longer with improved organ function and overall performance. A multicenter US/European retrospective study included 57 patients with SM. OS was especially good for SM-AHN (~70%) but poor for patients with MCL (<20%). Patients with ASM had survival rates between these 2 subsets. A recent study summarized 71 German patients with SM receiving allo-HCT between 1999 and 2021.[91] Most patients had SM-AHN (n = 52); the median age was 59 years. PFS and OS were 39% and 59%, respectively. Unfavorable risk factors for survival were the absence of a *KIT* mutation and complex cytogenetics. In the German study, the effect of KIT inhibitors before allo-HCT was positively correlated with survival. In both studies, patients who had responded at allo-HCT had better survival.[90] In both studies, total body irradiation had no significant impact. Although the study by Ustun et al[90] suggested a potential positive effect of using myeloablative conditioning, this was not demonstrated in the German study.[91]

Current challenges in the management of SM. Clinicians and patients now have access to effective drugs for both ISM and AdvSM (Figure 7; Table 2). Researchers are exploring systemic agents, such as KIT inhibitors[84] (bezuclastinib[92,93] and elenestinib),[85] Bruton tyrosine kinase inhibitors,[94,95] or mTOR inhibitors,[96] and topical agents such as cromoglicic acid in SM. Although this is a significant advancement, there are still challenges.

THE CHALLENGES IN THE MANAGEMENT OF ADVSM, INCLUDING SM-AHN. The management of AdvSM, particularly SM-AHN, presents significant challenges because of its heterogeneity. Patients with SM-AHN exhibit varying aggressiveness, with indolent variants and more aggressive forms. AHN also varies in aggressiveness, from low-risk MDS to very aggressive AML. The combination of these factors makes it often difficult to establish an optimal treatment plan in individual patients with SM-AHN.

In avapritinib and midostaurin studies, which primarily included patients with SM-AHN (~70%), excluded those with significant signs of disease considered as caused by AHN. Avapritinib is also contraindicated in patients with platelet counts of $<50 \times 10^3$ because of concerns about intracranial hemorrhage. These factors limit our understanding of real-world treatment strategies.

Histopathologic changes, such as liver fibrosis, have been observed in some patients with SM, despite normal serum liver function tests.[97] A French study confirmed these findings in 28 patients with SM, including 6 with ISM, 9 with ASM/MCL, and 13 with SM-AHN.[25] Fibrosis was observed in all groups, including 3 of 6 indolent SM cases and in most advanced SM cases. Interestingly, avapritinib decreased liver fibrosis.[97] These findings complicate current understanding of a C-finding indicating aggressive SM, and whether or not the aggressiveness of SM affects the management of these patients in the current era of effective KIT inhibitors.[97]

In managing SM-AHN, the classic approach focuses on treating the most aggressive component, such as AML in ISM-AML or ASM in ASM low-risk MDS. Although phase 2 studies showed the efficacy of KIT inhibitors in ASM low-risk AHN, their combination with other drugs (eg, hypomethylating agents, venetoclax, or low-dose anthracyclines) remains unknown regarding safety and efficacy. Similarly, no information is available on adding KIT inhibitors to conventional chemotherapies for the treatment of SM with aggressive AHN. Combining drugs is challenging because of safety concerns, especially some side effects (cytopenia with or without intracranial hemorrhage) are shared by KIT inhibitors and other agents.[76] Currently, only 1 study investigates a potential drug combination.[98]

Allo-HCT has been shown to be effective in controlling or curing both diseases in some patients.[90,91] It is indicated if warranted for the AHN component and should be considered for patients with SM-component resistance to KIT inhibitors. Similar to other hematologic malignancies, the outcomes of allo-HCT are superior in responsive patients.[90,91] Given the unpredictability of progression in SM-AHN[82] (Figure 6) and high mortality rates in patients who have progressed to AML-AHN, we believe that allo-HCT should be considered for most patients with SM-AHN (Figure 7; Table 3). In contrast, allo-HCT outcomes are not optimal in ASM and MCL, and survival rates have improved with small molecules and other drug therapies. These responsive patients likely do not require allo-HCT, although long-term outcomes are limited to 2 to 3 years. Judicious use of KIT inhibitors before allo-HCT for tumor reduction or treating stable or progressive disease after allo-HCT seems reasonable, but large data are missing.[99,100] However, pancytopenia, especially in the early phase after allo-HCT, is expected and a significant obstacle because of their mechanism of action. Guidelines for allo-HCT in AdvSM management exist and are likely subject to change in the dynamic era of SM management [99,101]

Cure may not be the primary goal as long as long-term disease control is achieved, as seen with BTK inhibitors in chronic lymphocytic leukemia and TKIs in CML. Predicting high KIT inhibitor progression risk, ideally shortly after therapy or diagnosis, is crucial such as *T315I* mutations in CML and *FLT3* mutations in AML. We are making some progress in our understanding of the mechanism

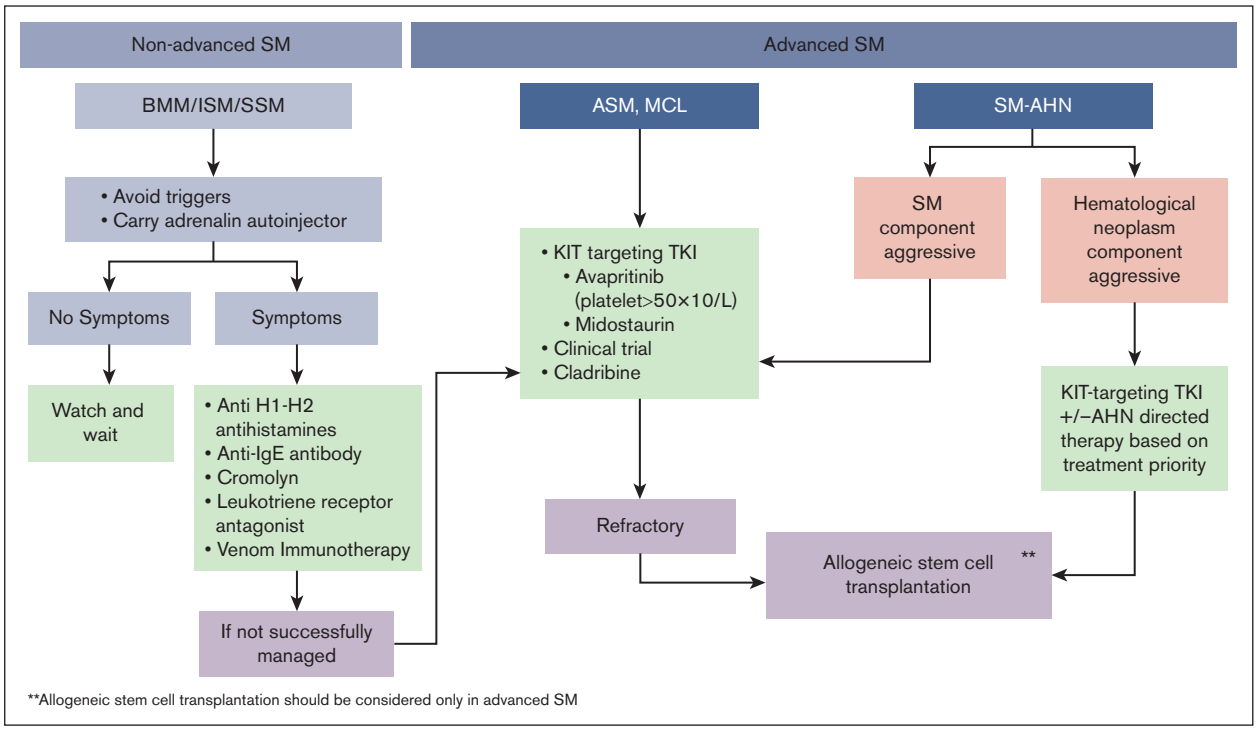

Figure 7. Treatment approaches of SM.

and rates of resistance to KIT inhibitors in SM. Patients with non-AdvSM with a higher *KIT* VAF level progressed more frequently when having received avapritinib.[69] Not yet published data (a conference presentation) suggest that RAS/MAPK pathways are more prominent in patients with relapsed/refractory AdvSM in avapritinib trials, with new mutations such as *NPM1* and *BCOR*, and even germ line mutations detected (*CHEK2*).[102] It also showed that progression of AHN to AML in SM-AHN has a poor prognosis (~80% mortality). Huang et al found the VAF of some mutations decreased with avapritinib treatment in 4 patients with ASM-AHN, whereas that of others increased.[103] These raise concerns about whether KIT inhibitors eliminate the main clone or simply delay progression.

THE CHALLENGES IN MANAGEMENT OF NONADVSM. KIT inhibitors revolutionize the treatment of patients with mastocytosis, but defining the optimal patient population is challenging. Factors such as QOL, symptom severity, response to antimediator medications, adverse effects from conventional polypharmacy, and cost of therapy should be considered before starting these medications. Clinically important adverse effects include fluid retention, vomiting, diarrhea, constipation, dysgeusia, cognitive changes, hair color loss, and mild-moderate cytopenia in patients with ISM. Although central nervous system bleeding occurred exclusively in AdvSM, complete blood count should also be monitored in nonAdvSM, although less frequently.

It is unknown whether these drugs reduce or prevent anaphylaxis; however, it might be reasonable to consider using KIT inhibitors for patients with ISM with life-threatening anaphylaxis, even in some patients with MC activation syndrome to reduce excessive MCs after lengthy discussions (off-label use).[104] Clearly, these patients should be included in studies to systematically analyze the drugs.

Table 3. Indication of allo-HCT

HCT indications in AdvSM A moving target		
Yes	**Gray zone**	**No**
1. AHN of SM-AHN requires allo-HCT 2. Progressive disease on modern, effective therapy • AHN is progressing or • SM is progressing	1. Inadequate response to modern, effective therapy in young patients A. Response by histopathology B. Response by biomarkers • KIT response (<25% at 6 mo) • Tryptase response (<50% at 6 mo) • ALP response (<50% at 6 mo) 2. Patients who have high risk of progression • Additional mutations (S/A/R)	1. Responsiveness of patients regarding SM component • CR • At least PR and response is deepening over time

Modern, effective therapy: midostaurin or avapritinib.
CR, complete response; PR, partial response; S/A/R, *SRSF2*, *ASXL1*, *RUNX1*.

Other potential indications include therapy-refractory symptoms or side effects from polypharmacy. In the PIONEER study, the number of drugs needed to control daily symptoms decreased over time, with 21% achieving this by 24 weeks and 31% by 4 weeks in the avapritinib arm.[105] This may support that longer-term exposures to KIT inhibitors are associated with more durable/deeper responses, as reported by the Mayo Clinic.[106]

What is the optimal duration of a KIT inhibitor? Should it be indefinitely continued until benefits outweigh risks? Does longer use induce deeper response or drug resistance? Even if the goal is indefinite, stopping may be unavoidable because of reproductive age risks and potential adverse effects on fetuses. High doses of avapritinib did not affect fertility in male or female rats, but mild hypospermatogenesis was observed in dogs.[107] Its effects on human fertility are unknown. A 34-year-old man with SM became a father after stopping avapritinib for a year.[107] Discontinuation is mandatory for pregnant individuals, so education on contraception is crucial.[108] Reducing dose or holding KIT inhibitors for parental desire may quickly worsen symptoms and biomarkers, but it is unknown.

Current ongoing mysteries

It is not uncommon for patients with substantial symptom burden to have a relatively low percentage of MCs (<5% in the BM). Likewise, a significant reduction (>50%) in objective findings with an effective KIT inhibitor may not produce, although statistically significant, the same degree of reduction in symptoms. In the PIONEER phase 2 trial, avapritinib reduced tryptase levels by >50% in 54% of patients in 6 months, compared with 0% in the placebo group; similar positive results were observed for *KIT* VAF and BM MC percentage.[109] Although the improvement in symptoms was statistically significant, the difference compared to placebo was small. Avapritinib-treated patients had a decrease in mean total symptom score (TSS) of 15.6 points compared with a decrease of 9.2 points in the placebo group. Some QOL assessments showed limited improvements compared with placebo; the 12-item Short-Form Health Survey (SF-12) physical scores increased by 20% vs 12%.[109] However, objective and subjective improvements were close to each other with bezuclastinib. In the phase 2 double-blinded study (n = 24) in which bezuclastinib was compared with placebo, there were significant improvements in both objective findings and symptoms; tryptase levels were reduced by >50% in 88% of patients in the bezuclastinib arm vs 0% in the placebo arm. Based on patient-reported symptoms, mastocytosis symptom severity daily diary (MS2D2) TSS decreased by 23.7% with bezuclastinib vs 9% with placebo. According to early reports, 70% of patients who had received bezuclastinib achieved a reduction in TSS of >50% at 3 months, compared with 8% of those who received a placebo.[110] Moreover, some symptom groups may respond better (skin, allergic reactions) than others (GIT) in avapritinib trials.[111] How to interpret these results? Are some symptoms not caused by abnormal MCs? Are responses to all KIT inhibitors not universal because of drug properties?[110] Are the differences simply caused by variance in the patient populations, or is it also possible that KIT inhibitors alone are not adequate to completely control disease in all patients? It is probable that combining KIT inhibitors with other groups of drugs with different mechanisms of action is needed. A new study is exploring a novel BTK inhibitor in ISM.[112]

What are the exact mechanisms of bone changes in SM? One of the most common findings in nonAdvSM is osteopenia/osteoporosis, which appears to be unrelated to tumor burden.[113] In AdvSM, in fact, increased bone density and osteosclerosis are common.[113] Management with standard osteoporosis medications (eg, vitamin D, calcium replacement) may be ineffective. Bisphosphonates (eg, zoledronic acid)[114] and denosumab, a RANKL inhibitor, have shown some promising efficacy in case reports.[115,116] The impact of KIT inhibitors on osteoporosis has yet to be analyzed.

Response evaluation

Various definitions of organ damage and response to treatment criteria remain a challenge, particularly in SM-AHN. The Valent criteria defines 3 main responses: major response, partial response, and no response, based on C-findings.[6,7] The International Working Group and European Competence Network on Mastocytosis also provided detailed definitions for various categories of organ damage, including a reduction in serum tryptase levels, the elimination of MC aggregates in the BM (or other extracutaneous organs), and PB count recovery.[117] Recently, pure pathologic response criteria based on BM MC burden, *KIT* mutation VAF, and serum tryptase level (excluding consideration of organ damage) have been proposed.[118,119]

Conclusion

Oncologists, hematologists, allergists, gastroenterologists, endocrinologists, dermatologists, and hematopathologists in the community and in academia have made significant strides in SM. Many patients with AdvSM can achieve long-term, progression-free phases with TKI therapy, chemotherapy, or allo-HCT. Available data suggest that novel KIT TKIs are also useful for symptom control in patients with SM. Future research will focus on optimizing drug use (maybe in combinations), safety, and cost-effectiveness, considering the limited resources. Raising awareness and fostering collaborations among stakeholders will aim to enhance outcomes and QOL for patients with SM.

Authorship

Contribution: C.U., F.K.K., P.V., M.A.L., and C.A. performed literature search, collected data, and wrote and edited the manuscript.

Conflict-of-interest disclosure: C.U. reports receiving honoraria for speakers' bureau participation from Blueprint and Sanofi. P.V. reports receiving research support from AOP Orphan and Pfizer; and honoraria from Blueprint, Bristol Myers Squibb/Celgene, Cogent, Incyte, Novartis, Pfizer, Servier, and Stemline. C.A. has consultancy agreements with Blueprint, Cogent, Allakos, and Novartis; and receives research support from Blueprint and Cogent. The remaining authors declare no competing financial interests.

ORCID profiles: C.U., 0000-0001-6896-6213; F.K.K., 0000-0001-6078-5944; M.A.L., 0000-0002-0830-5453; P.V., 0000-0003-0456-5095; C.A., 0000-0001-6301-4520.

Correspondence: Celalettin Ustun, Division of Hematology Oncology and Cellular Therapy, Department of Medicine, Rush University, 1725 W Harrison St Suite 304, Chicago, IL 60612; email: celalettin_ustun@rush.edu.

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