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Relevant updates in systemic mastocytosis

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ABSTRACT

Systemic Mastocytosis (SM) is a rare myeloproliferative neoplasm (MPN) that is characterized by a clonal proliferation of mast cells (MCs). The symptoms and clinical presentation of SM are the result of both MC proliferation as well as activation and degranulation, causing hyperactive and over-exaggerated hypersensitivity responses, as well as organ infiltration by pathogenic MCs. The clinical presentation and course of SM is varied and organ involvement can lead to significant morbidity and mortality in some cases. The subtypes of SM include indolent SM (ISM), smoldering SM (SSM), aggressive SM (ASM), SM with associated hematologic neoplasm (SM-AHN) and mast cell leukemia (MCL) and survival can range from normal in the case of ISM to months in MCL. The treatment of indolent forms of SM is largely focused on addressing symptom burden (B findings), while cytoreductive agents and more recently molecularly targeted agents are employed to reduce MC burden and reverse associated organ dysfunction (C findings). Although the pathogenesis of SM is multi-factorial, the acquisition of *KIT* D816 V is a relatively frequent mutational event and serves as the target of novel agents. The recent approval of midostaurin for the treatment of advanced SM has brought awareness to this disease and energized further drug development efforts. Expanding our understanding of the underlying molecular mechanisms of SM will continue to inform future therapeutic approaches.

1. Introduction

Systemic mastocytosis is a myeloproliferative neoplasm (MPN) characterized by the clonal proliferation of mast cells (MCs) and their subsequent infiltration of either the bone marrow (BM) or extracutaneous, extramedullary sites. SM is relatively less common than other MPNs such as polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF), and was only first defined by the World Health Organization (WHO) in 2001 [1,2]. The different subtypes of SM, which carry important clinical and diagnostic implications, are delineated by the presence or absence of WHO-defined 'B' and 'C' findings, which aim to describe the degree of bone marrow and reticuloendothelial involvement. Given its rarity, non-specific symptomatology, and relatively recent diagnostic standardization, the current treatment approach is somewhat limited, but rapidly evolving. Here we will briefly describe the pathogenesis, epidemiology and diagnosis of SM and, thereafter, attempt to deliver a detailed update on the current available treatments and future therapies in development.

2. Background and epidemiology

MCs were first described in the 1870s by Paul Ehrlich [3] and belong to the subset of hematologic cells that are derived from the granulocyte/monocyte lineage [4,5]. MC progenitors are released from the BM whereby they migrate to peripheral tissues and mature, where they mediate allergic and anaphylactic reactions via degranulation and release of inflammatory and vasoactive cytokines and chemokines [6,7]. Much like other cells derived from the granulocyte/monocyte lineage (such as neutrophils, basophils and eosinophils), MC maturation is reliant on a number of regulatory chemicals and cytokines. These regulatory mediators and activators, and their cognate receptors expressed on the surface of MCs, such as IL-33 [8], IgE/ FcεRI [9], and KIT ligand/CD117 [10], are important therapeutic targets. Of particular therapeutic importance is *KIT* D816 V, which improved technologies, such as real-time quantitative PCR, have demonstrated to be present in the majority of patients with SM.

Mastocytosis, defined by the abnormal expansion of clonal MC in the BM and peripheral tissues, can be broadly separated into two distinct clinical entities – cutaneous mastocytosis (CM) and SM. Localized MC tumors, which are rare, can be classified as either a manifestation of

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Table 1
2016 WHO Classification of Mastocytosis.

Disease	Disease subset
Cutaneous Mastocytosis	Urticaria Pigmentosa
	Diffuse Cutaneous Mastocytosis
	Mastocytoma of Skin
Systemic Mastocytosis (SM)	Indolent SM
	Smoldering SM
	Aggressive SM
	SM Associated Hematologic Neoplasm
	Mast Cell Leukemia
Mast Cell Sarcoma	

SM or a separate, third entity (Table 1). CM and SM differ in the sites of MC infiltration, with mastocytosis in CM relegated to skin involvement as opposed to the multi-organ involvement observed in SM.

The first description of mastocytosis in the scientific literature was made by Nettleship and Tay in their 1869 case report of a young girl with urticaric skin lesions, which was later termed urticaria pigmentosa (UP) by Sangster in 1878 [11,12]. A few years after Sangster coined the term for this novel dermatologic condition, biopsies of similar, isolated urticarial lesions revealed the infiltration of MCs [13]. The term mastocytosis was first used by Sézary only in the early 1930s and was originally thought to involve only the skin [14]. It wasn't until 1949 that an autopsy of a patient with known UP revealed systemic MC infiltration that the entity of SM was described [15].

CM is most commonly an indolent, pediatric disease with a favorable prognosis [16]. Per the most recent WHO classification, CM can be divided further into maculopapular CM, more commonly referred to as UP, diffuse CM and localized mastocytoma of skin [17]. UP is the most common presentation of CM in children – it frequently presents before the age of 6 months and accounts for approximately 70–90% of reported cases [16,18]. Localized cutaneous mastocytomas, which are commonly present at birth or develop within the first week of life, account for a smaller percentage of CM, approximately 10–35% of cases. Diffuse CM is rare in comparison with the other two subsets of CM, and accounts for approximately 1–3% of reported cases18]. The prevalence of CM in the United States has been reported as a range of 1:1000 to 1:8000 [19], though this statistic is derived from relatively older data and may be biased by the lower recognition of the disease at that time. Newer, mostly European studies estimate a higher disease prevalence of CM, on the order of 1:200 to 1:800 pediatric dermatology patients [20,21]. The disease may have a slight male predominance, although some epidemiologic studies report a minor female predominance in certain geographic locations [20–22]. The majority of CM cases develop without an associated family history, though many reports of suspected familial cases are described, and a small genetic component to the disease may well indeed contribute22].

Whereas CM is relatively uniform in its favorable prognosis, SM is a more nuanced disease entity. SM is composed of 5 subtypes (from favorable to poor prognosis): indolent SM (ISM), smoldering SM (SSM), SM with an associated hematologic neoplasm (SM-AHN), aggressive SM (ASM) and mast cell leukemia (MCL) [17]. Studies describing the epidemiology, incidence and prevalence of SM are sparse, likely due to a combination of its rarity and obscure clinical presentation, which will be discussed further. Cutaneous lesions may be associated with SM, and the disease is predominantly one of the adult population, as opposed to CM which is common in the pediatric population. SM, as a whole, is associated with a poor prognosis, with a median survival of approximately 5 years [23]. Notably, the prognosis of SM varies widely across different subtypes, with ISM associated with a similar life expectancy to the general population, versus MCL, which has an overall median survival on the order of months.

Although significant epidemiologic data from the US population is lacking, ISM is considered to comprise upwards of 90% of all cases of SM [24]. The estimated prevalence of SM in the US population is 20,000–30,000 individuals, with a slight male and Caucasian predominance [25]. In a Danish population study published in 2014 using the National Pathology Registry and National Cancer Registry databases, SM had a prevalence of 9.29 persons per 100,000 [26]. ISM was the most prevalent subtype of SM, which accounted for 82% of total cases. SM with an unknown subtype was the next most prevalent disease subtype, accounting for 11% of total cases. SM-AHN (most commonly plasma cell dyscrasias, MDS and AML), ASM and MCL accounted for 4%, 2% and 1% of all cases, respectively. In this same study, diagnosis of SM occurred at a median age of 49.6 years with a slight female predominance (59.9% of patients) [26].

3. Clinical and laboratory findings

The clinical symptoms of SM result from MC proliferation and the local and systemic effects of MC mediators, such as amines (e.g. histamine), proteases (e.g. tryptases) and cytokines such as TNF-alpha, interleukin-4, stem cell factor and others [27]. The most commonly affected organ systems include the skin and the gastrointestinal tract, although patients may experience cardiovascular involvement with palpations and tachycardia, respiratory involvement with wheezing or other asthmatic symptoms, neurologic deficits such as decreased cognition, and cortical bone involvement commonly manifesting as osteoporosis as well. In advanced SM, BM infiltration may result in marked peripheral cytopenias, and consequently increase the risk for bleeding or infectious complications. In a case series of 21 patients with SM treated at the Brigham and Women's Hospital in Boston with a median follow-up of 5.9 years, episodic flushing was the most commonly noted symptom, occurring in 20 patients [28]. Headaches were the most common presenting symptom with 19 patients reporting frequent, bilateral headaches. Twelve patients reported rhinitis, and 2 reported wheezing attacks noted to correlate with exacerbations of their disease. Finally, gastrointestinal symptoms were prevalent and debilitating. Seventeen patients reported significant episodes of abdominal pain, 12 reported intermittent episodes of nausea and vomiting, and 5 patients had pathologic inflammation (e.g. esophagitis, gastritis, peptic ulcer disease) confirmed on endoscopy. The neuropsychiatric symptoms associated with SM are varied, and can include depression, anxiety, memory loss, cognitive impairment and "brain fog," the latter of which corresponds to a vague, but frequent, constellation of findings including problems with focus, attention, short-term memory and ability to multitask [29].

Cutaneous findings may be seen in patients with SM. In patients with advanced SM, significant organopathy resulting from MC infiltration may be observed. While any organ may be affected, the most common are liver, spleen and gastrointestinal tract [30]. More advanced SM may likewise be associated with clinical findings of lymphadenopathy, pathological fractures due to bone demineralization, and malabsorption and cachexia in later stages.

Laboratory findings help to both establish a diagnosis of SM and grade severity. In a series of 342 patients with SM referred to the Mayo Clinic, 19% of patients had a hemoglobin < 10.0 g/dL, 15% had an absolute eosinophil count $\geq 1.5 \times 10^9$/L, and 20% had a platelet count $< 100 \times 10^9$/L. The prevalence of significant cytopenias was significantly higher in ASM and SM-AHN rather than ISM. Elevations in alkaline phosphatase, total bilirubin, AST and ALT were documented in 40%, 22%, 12% and 10% of patients, respectively. Serum tryptase, which may act as a potential diagnostic marker for SM, was elevated in almost all patients (96%), although a significant elevation (≥ 200 ng/mL) was statistically more common in patients with ASM and SM-AHN [23]. On BM examination, age-adjusted cellularity, fibrosis, and blast percentage were all significantly higher in patients with more aggressive disease subtypes. Interestingly, the BM MC percentage was not significantly different between any disease subtypes. Finally, cytogenetic analysis demonstrated a higher prevalence of karyotypic

abnormalities among ASM and SM-AHN versus ISM, and molecular studies demonstrated *KIT*D816 V and *JAK2*V617 F (mutant allele burden > 1%) mutation frequencies of 68% and 4%, respectively [23].

4. Diagnosis and staging

The WHO classification of mastocytosis, including all subsets of CM and SM, were recently updated in 2016. Given the scope of this article, only the updated diagnostic and staging criteria for SM will be discussed in depth. The 2016 WHO updated criteria for CM adopted the proposed 2001 classification scheme by Valent et al that divided the disease into maculopapular CM, diffuse CM and mastocytoma of skin, which have been previously discussed [1,17,31].

The original WHO classification of mastocytosis subdivided SM into 4 different disease phenotypes – ISM, SM-AHN, ASM and MCL [32]. The updated 2016 WHO classification of mastocytosis added a fifth subgroup of SM, SSM, which was included in the original classification proposal by Valent et al in 2001 [1]. Notably, SSM had been proposed almost a decade earlier as an additional subvariant disease in 2007 by a separate EU-US consensus group [33]. Additionally, the most recent WHO classification further subdivides ASM into an untransformed variant and a variant "in transformation to MCL", which can also be referred to as ASM-t, based on an earlier proposal by an EU-US consensus group [34]. The relationship between ASM, ASM-t and MCL is very much analogous to the WHO classification for MDS, MDS-EB and AML, where ASM-t is defined by BM smears with ≥ 5% but less than 20% MCs (with > 20% MCs defining MCL) and represents a subvariant more likely to progress to a leukemic state. Finally, the 2016 WHO classification system updated the definition of MCL to include both an acute and chronic form, the former being defined by the presence of "C-findings," which will be defined shortly.

The major criterion for diagnosing SM is the demonstration of multifocal, dense infiltrates of MCs (defined as ≥ 15 MCs in aggregates) in BM biopsies and/or sections of other extracutaneous organs. The WHO 2016 guidelines for diagnosing SM require the fulfillment of this major criterion and at least 1 additional minor criterion. SM may still be considered without this finding, if 3 or more minor criteria are present, which are defined by: MC dysplasia in the BM or extracutaneous organs, the presence of the *KIT* point mutation at codon 816, flow cytometry demonstrating MCs staining positive for CD2 and/or CD25, and a baseline elevation in serum tryptase level (Table 2).

Delineation of SM subvariants is dependent on the presence or absence of associated "B-findings" and "C-findings," which are unchanged in the recent WHO update. Briefly, B-findings are indicative of a high burden of MCs and involvement of multiple hematopoietic lineages, whereas C-findings are not only indicative of an abnormally high MC burden, but resultant organ damage or dysfunction (Tables 3 and 4).

5. Treatment and prognosis

5.1. ISM

ISM is the most common subvariant of SM and carries the most favorable prognosis [35]. Patients with SM who have less than 2 B-findings and no C-findings meet diagnostic criteria for ISM. Although transformation from ISM to a more aggressive subvariant of SM is possible, retrospective data has shown this to be a relatively rare phenomenon [36]. Possible serum markers prognosticating an increased risk of transformation include an elevated β2-microglobulin and the presence of *KIT* mutations in mast cell, myeloid and lymphoid hematopoietic lineages. Even with a low risk of transformation to a more aggressive disease subvariant, the overall survival for ISM is not significantly different from the age- and sex-matched US population [23].

Management of ISM is focused on both the prevention and treatment of MC-mediated hypersensitivity reactions. Avoidance of certain known triggers is an important lifestyle modification for patients with ISM. Common allergens include pollen, dander, certain foods such as dairy products, dust mites, insects, molds and medications such as NSAIDs, B-lactam antibiotics and opiates [37]. A particular trigger of interest to patients with SM is anesthetic agents, which can cause anxiety for patients who require surgical procedures. Although anesthetics have been associated with triggering anaphylactic reactions in patients with SM, this data is largely derived from case reports and limited clinical experience. The largest retrospective study to examine the effects of anesthesia in SM included over 500 pediatric and adult patients in the setting of procedures utilizing anesthesia. In total, 4% of children and 2% of adults moderate perioperative MC mediator-related symptoms, and 2% of children and 0.3% of adults had an anaphylactic reaction. Overall, there was no correlation between the likelihood of a reaction and the type of anesthetic used, although patients who received prophylactic anti-mediator therapy with antihistamines had a lower rate of MC mediator-related symptoms [38].

Anaphylactic reactions, which can include profound tachycardia and hypotension, may be more severe and fatal in patients with SM versus the general population [39]. A retrospective case series of 120 German children and adults with mastocytosis observed a cumulative incidence of anaphylactic reactions of 56% in those with SM, with 48% of those reactions being classified as severe and 38% resulting in unconsciousness [40]. Epipens, ready-to-inject formulations of epinephrine, should be prescribed to all patients with known mastocytosis in case of an anaphylactic reaction to a new or unavoidable trigger,

Table 3
and C findings in Systemic Mastocytosis (SM).

B and C Findings in SM
B-Findings
1 MC infiltration grade in the bone marrow (BM) > 30% by histology and basal serum tryptase level > 200 ng/ml
2 Hypercellular BM with loss of fat cells, discrete signs of dysmyelopoiesis without substantial cytopenias or WHO criteria for an MDS or MPN
3 Organomegaly: palpable hepatomegaly, palpable splenomegaly, or palpable lymphadenopathy (on CT or ultrasound: > 2 cm) without impaired organ function
C-Findings
1 Cytopenia(s): Absolute neutrophil count < 1,000/μL or hemoglobin < 10 g/dL or platelets < 100,000/μL
2 Hepatomegaly with ascites and impaired liver function
3 Palpable splenomegaly with associated hypersplenism
4 Malabsorption with hypoalbuminemia and weight loss
5 Skeletal lesions: large-sized osteolyses with pathologic fractures
6 Life-threatening organ damage in other organ systems that is caused by local mast cell infiltration in tissues

Table 2
WHO 2016 Systemic Mastocytosis (SM) Diagnostic Criteria.

Major SM Criterion	Multifocal dense infiltrates of mast cells (MCs, 15 MCs in aggregates) in bone marrow (BM) biopsies and/or in sections of other extracutaneous organ(s)
Minor SM Criteria	a. > 25% of all MCs are atypical cells (type I or type II) on BM smears or are spindle-shaped in MC infiltrates detected on sections of visceral organs
	b. KIT point mutation at codon 816 in the BM or another extracutaneous organ
	c. MCs in BM or blood or another extracutaneous organ exhibit CD2 and/or CD25 positivity
	d. Baseline serum tryptase level 20 ng/mL^{+}

*If at least 1 major and 1 minor OR 3 minor SM criteria are fulfilled, the diagnosis of SM can be established.
$^{+}$In case of an unrelated myeloid neoplasm, item d is not valid as an SM criterion.

Table 4
Diagnostic Criteria for Subtypes of Systemic Mastocytosis (SM).

Disease	Diagnostic Criteria
Indolent SM	SM with less than 2 B-Findings and no C-Findings
Bone Marrow Mastocytosis	SM with less than 2 B-Findings and no C-Findings AND lack of cutaneous symptoms
Smoldering SM	Two or more B-Findings but no C-Findings
SM-Associated Hematologic Neoplasm	Separate fulfillment of SM diagnostic criteria and another hematologic syndrome
Aggressive SM (ASM)	One or more C-Findings (with or without additional B-Findings) with $<$ 10% peripheral MC and $<$ 20% BM MC infiltration
Transforming ASM	ASM criteria with AND MC % in BM smears is $>$ 5% but $<$ 20%.
Mast Cell Leukemia (MCL)	One or more C-Findings (with or without additional B-Findings) with $\geq$ 20% BM MC burden
Aleukemic MCL	MCL criteria and peripheral MC burden $<$ 10%
Acute MCL	MCL criteria and no obvious organ damage (no C-findings present)
Chronic MCL	MCL criteria and obvious organ damage (C-findings present)

such as hymenoptera stings.

Antihistamines are employed across all variants of SM and are considered first-line for the treatment of most common symptoms [41]. H1 blockade with agents such as diphenhydramine are useful for pruritus while H2 blockade with agents like famotidine and ranitidine may be useful for GI symptoms [33]. Topical formulations of H1 antihistamines may be employed in cases of pruritus or skin blistering without other significant symptoms, in order to obviate the need for systemic therapy.

Aspirin may act to either exacerbate symptoms of mastocytosis, via induction of MC degranulation, or to treat symptoms of mastocytosis via cyclooxygenase inhibition of prostaglandin production. Reported incidences of aspirin intolerance among patients with SM range from 5 to 10% [42,43]. In order to assess for aspirin intolerance, it may be prudent to start in low doses, with the concurrent use of antihistamine prophylaxis [44]. A retrospective review of aspirin use in SM (19 cases of ISM and 1 case of SM-AHN) found that maintenance doses of aspirin between 81 mg and 500 mg twice daily, significant lower than previously reported therapeutic doses for SM, were sufficient to significantly decrease prostaglandin levels, though clinical benefit was not ascertained [45].

Antileukotrienes, cromolyn sodium, and omalizumab can be used either as adjunctive therapies or second- or third-line treatments. Leukotriene excretion is increased in patients with SM and is thought to contribute to MC-mediated symptoms [46]. Although mechanistically logical, the recommendation for antileukotriene use in SM is based solely on expert opinion and limited case reports [47,48]. Cromolyn sodium, an inhibitor of MC activation, has been demonstrated in multiple placebo-controlled trials to improve disease activity in SM [49,50]. Omalizumab, a monoclonal antibody that binds to free IgE and is FDA approved for the treatment of moderate-to-severe persistent asthma and chronic idiopathic urticaria, has been demonstrated to reduce symptom burden and successfully treat unprovoked anaphylaxis in multiple case reports [51,52].

Certain patients may require the use of glucocorticoids, administered either topically or systemically. Glucocorticoids may be particularly useful in the treatment of SM for acute allergic reactions, though their use is limited by long-term adverse effects. Phototherapy has been demonstrated to be an effective adjunctive treatment for UP and cutaneous symptoms [53,54]. Cutaneous manifestations may also respond to topical emollients and calcineurin inhibitors.

Musculoskeletal manifestations are common as MC infiltration of the BM leads to osteopenia and osteoporosis. Approximately 25% of patients with mastocytosis will experience some degree of musculoskeletal pain and approximately half of adult patients with SM have some degree of osseous involvment [55,56]. All patients should have an initial DEXA scan, with follow-up imaging determined by initial results. The treatment of osseous complications of SM is similar to that of the general population. Bisphosphonates have documented effectiveness in osteoporosis caused by mastocytosis [57], and vitamin D and calcium supplementation may be given to patients with osteopenia [58].

The use of cytoreductive agents and disease-modifying therapies, which are associated with significant adverse effects and varying degrees of mutagenicity, is often not indicated in patients with ISM. Exceptions to this rule may be made for patients with ISM and rapidly evolving or particularly burdensome B-findings that may require more aggressive treatment.

ISM rarely progresses to a more aggressive form of SM. In a Spanish cohort study, only 5 (3%) of 145 patients with ISM progressed to a more aggressive disease after a median of 147 months of follow-up [36]. Still, regular follow-up is important to document trends in peripheral blood counts and liver function, and to ensure that symptoms are being adequately treated. Serum tryptase levels and *KIT* D816 V allele burden have been demonstrated to correlate with disease progression and activity, and it is useful to follow tryptase levels at least yearly as a marker for disease activity [59,60].

5.2. SSM

SSM, which was added to the WHO classification of SM in 2016, was previously defined as a subtype of ISM. Whereas patients with ISM display less than 2 of the pre-specified B-findings, patients with SSM display 2 to 3 B-findings without any C-findings [1]. SSM may confer a higher rate of transformation to a more aggressive disease variant, and is associated with an increased symptom burden compared to ISM. Patients with SSM tend to be older than patients with ISM, perhaps reflecting a natural history of the disease course to progress over time. Patients in the aforementioned series by Lim, et al were more likely to present with constitutional symptoms, anemia, and elevated MC mediator levels if they were diagnosed with SSM versus ISM [23]. Patients with SSM have a significantly shorter OS when compared to patients with ISM, resulting from either their advanced age or increased risk of disease transformation. The overall risk of transformation to ASM or acute leukemia is approximately 15–20% in patients with SSM, significantly higher than compared to patients with ISM [23]. Patients with SSM should be regularly followed and assessed for transformation to more aggressive disease variants, and serum tryptase, which may be used to assess disease response, may be evaluated biannually to monitor disease activity and appropriately adjust therapy [61].

Therapeutic strategies in SSM are largely similar to those in ISM, with an emphasis on symptom management as opposed to disease-modifying therapy. Avoidance of known triggers, prophylactic prescription of an epi-pen, and medications such as anti-histamines, antileukotrienes, cromolyn sodium, omalizumab and aspirin may all have a role in the prevention or treatment of MC-mediated symptoms. Cytoreductive therapy may be required for patients with SSM that is associated with particularly burdensome B-findings such as obtrusive splenomegaly, or for patients who experience frequent anaphylactic reactions that are poorly controlled with preventive or abortive therapy [62].

Interferon-alpha (IFN-α) was first posited as a possible disease-modifying agent for SM in the early 1990s, based on its efficacy in other

MPNs, such as chronic myelogenous leukemia (CML) [63]. IFN-α has been administered with or without corticosteroids, without significant differences in outcomes between the two regimens. ISM and SSM are poorly represented in most cytoreductive SM trials, but patients with these disease variants have demonstrated overall response rates (ORR) of approximately 50% in such studies [64,65]. For ISM/SSM, responses to IFN-α typically consist of a decreased MC-mediated symptom burden, resolution or reduction in UP and other cutaneous findings, and a decreased BM MC burden65]. IFN-α tends to be poorly tolerated, and may compound manifestations of SM, such as depression and cytopenias.

Cladribine (2-chlorodexoyadenosine, 2-CdA) was first described as an effective second-line therapy for a patient with SM who was intolerant of IFN-α in 2001 [66]. A follow-up, phase II, study of 9 patients with SM were treated with cladribine, and the 3 patients with ISM/SSM demonstrated a significant reduction in symptoms [67]. A French, multi-center study consisting of 44 patients, half of whom had ISM/SSM, demonstrated particular efficacy with 2-CdA in this setting, with an ORR > 90%, versus only 58% for ASM [68]. For this reason, some experts recommend 2-CdA as a first-line therapy for SSM when disease-modifying therapy is indicated [17].

In recent years, the use of tyrosine kinase inhibitors (TKIs) in SM has rapidly expanded due to the high prevalence of acquired gain-of-function mutations in the gene encoding the tyrosine kinase *KIT*, which result in uncontrolled cellular proliferation [69]. The most common *KIT* somatic mutation in SM is the point mutation KIT^{D816V}, which is present in greater than 95% of SM-AHN, ASM and ISM, and approximately 70% of MCL [70]. Notably, many other activating point mutations of *KIT* have been identified in SM, though with considerably lower prevalence [69].

Imatinib was the first TKI evaluated in SM, due to its notable efficacy in CML and mutant-*KIT* gastrointestinal stromal tumors [71,72]. However, studies soon demonstrated that the KIT^{D816V} mutation conferred resistance to imatinib, and the drug displayed limited efficacy in clinical trials [73,74]. Imatinib is approved by the Food and Drug Administration (FDA) for SM without, or with an unknown, KIT^{D816V} mutation, and may be particularly effective in patients with an increased MC burden associated with *FIP1L1/PDGFRA* + neoplasms [75]. Second and third generation TKIs, such as dasatinib and nilotinib, are effective *in vitro* against KIT^{D816V} mutations, but appear to have limited clinical efficacy with phase II trials demonstrating ORRs of 20–30% [76,77].

Midostaurin, a multi-kinase inhibitor, whose targets include both wild-type and KIT^{D816V}, is approved by the FDA for advanced SM [78]. The efficacy of midostaurin in ISM/SSM is less well-established, as this drug has been studied primarily for advanced disease [79,80]. A Dutch phase II trial recently evaluated the efficacy of midostaurin for 20 patients with ISM or SSM and reported significant reductions in symptom burden and tryptase levels after 24 weeks of treatment [81]. Mastitinib, another multi-kinase inhibitor, has demonstrated efficacy in the treatment of more indolent mastocytosis. A recent multi-national, randomized, placebo-controlled study of 135 patients with either ISM or SSM found a significantly decreased symptom burden and tryptase level with mastitinib versus placebo after 24 weeks [82]. Although no direct comparison of midostaurin and mastitinib for ISM/SSM exists, a *post hoc* analysis done by Anrooij et al reported that midostaurin appeared more effective in this setting [81].

5.3. SM-AHN

SM-AHN is the second most common subvariant of SM, accounting for approximately 30–40% of all cases [83]. The diagnosis of SM-AHN requires that a patient fulfills WHO criteria for both SM and an associated hematologic neoplasm, though an elevated tryptase level may not be used as a minor criterion in this setting [2]. The associated neoplasm is most often myeloid in lineage, though lymphoid (typically B-cell) and plasma cell neoplasms have been documented with appreciable frequency [33]. SM-AHN has a poor prognosis compared with other disease variants, and OS depends primarily on the associated malignancy. Median OS in the largest documented case series was approximately 2 years, although SM-MPN patients had a significantly longer median survival (31 months), as compared with SM-CMML (15 months), SM-MDS (13 months) or SM-acute leukemia (11 months) [84].

Patients with SM-AHN should be treated for both their SM and associated neoplasm. It is important to consider the AHN as secondary to the development of SM, which confers a poor prognosis similar to therapy-related or MPN/MDS-transformed leukemia [62,85]. Therefore, patients with SM-AHN should be treated as having high-risk disease, as are patients with transformed hematologic disease. Those patients who are able to achieve a complete remission of their AHN, or exhibit a significant disease response after treatment, should be considered for allogeneic stem cell transplantation (alloSCT)[86] to consolidate their response.

It is difficult to quantify the relative contribution of mastocytosis to typical B- and C-findings in patients with SM-AHN, and these patients are often treated as having aggressive disease. The treatment options for SM in this setting are similar to those for ASM, which will be discussed in the following section. Treatment for SM and the associated neoplasm may overlap, most notably with the increased utilization of midostaurin for *FLT3*-mutated AML. Of note, hydroxyurea may be a specific agent to avoid in SM-AHN. A retrospective analysis of patients treated at the Mayo Clinic that included 28 patients with SM-AHN treated with hydroxyurea reported an ORR of 19%, mostly related to partial responses in the hematologic neoplasm component of the disease [65].

5.4. ASM

Patients with SM and 1 or more associated C-findings (which demonstrate significant organopathy or MC BM infiltration) meet WHO diagnostic criteria for ASM. Prior to 2016, ASM was characterized as either slowly progressing or rapidly progressing, based upon the time course of end organ function and change in serum tryptase levels [1]. ASM is relatively rare compared to ISM/SSM and SM-AHN, only accounting for 12% of patients in the largest documented case series [23]. Median OS for patients with ASM in this study was 41 months, though only 2 of 41 patients transformed to acute leukemia. Response criteria for advanced SM, which includes ASM, SM-AHN and MCL, can be found in Table 5.

Patients with slowly progressing ASM are recommended for first-line disease modifying therapy with IFN-α or cladribine [17]. The recommendation for IFN-α in this setting comes from a combination of its documented efficacy ASM and its minimal mutagenicity [29,87,88]. Steroids may be a particularly effective adjunctive treatment in those patients with ascites, and prednisolone can be started prior to IFN-α and slowly tapered off after an observed response [44,62]. Alternatively, 2-CdA has well-documented efficacy for ASM [65,89]. A French study reported an ORR of 43% and a median duration of relapse-free survival (RFS) of 2.5 years for patients with ASM treated with 2-CdA, which was not significantly different from the median RFS of patients with ISM or SM-AHN [90]. Patients with slowly progressing ASM who do not respond to treatment with IFN-α or 2-CdA may be candidates for TKI therapy [91]. Imatinib may be used for patients without a detectable KIT^{D816V} mutation or an unknown mutational status (this applies to only approximately 10% of patients).

Midostaurin was approved by the FDA in 2017 for the treatment of ASM, largely based on the positive results of a 2016 open-label, phase II study published the year prior by Gotlib et al [79]. The study included 89 patients with advanced SM (16 ASM, 57 SM-AHN, and 16 MCL) treated with starting doses of 100 mg twice daily of midostaurin. The response rate for the primary efficacy population in the study was 60%, and the median response duration (of those who exhibited a response)

Table 5
2013 IWG-MRT-ECNM Aggressive Systemic Mastocytosis (SM), SM-Associated Hematologic Neoplasm and Mast Cell Leukemia Response Criteria.

Response	Criteria
Complete Remission (CR) *Requires all 4 criteria and response duration must be ≥ 12 weeks*	• No presence of neoplastic mast cell aggregates in the bone marrow (BM) or other biopsied extracutaneous organ • Serum tryptase level < 20 ng/mL (if the pretreatment serum tryptase level is ≥ 40 ng/mL) • Absolute neutrophil count ≥ 1 × 109/L, hemoglobin ≥ 11 g/dL, and platelet ≥ 100 × 109/L • Complete resolution of palpable hepatosplenomegaly and all biopsy-proven or suspected SM-related organ damage
Partial Remission (PR) *Requires all 3 criteria and response duration must be ≥ 12 weeks, in the absence of both CR and PD*	• Reduction by ≥ 50% in neoplastic mast cells (MCs) in the marrow and/or or other extracutaneous organ • Reduction of serum tryptase level by ≥ 50% (if the pretreatment serum tryptase level is ≥ 40 ng/mL) • Resolution of 1 or more biopsy-proven or suspected SM-related organ damage
Clinical Improvement (CI) *Response duration must be ≥ 12 weeks*	• Requires 1 or more pre-defined non-hematologic (improvement or resolution of ascites, pleural effusion, hypoalbuminemia, splenomegaly) and/or hematologic response criteria (improvement in a peripheral cytopenia) to be fulfilled in the absence of both CR, PR or PD
Stable Disease (SD)	• Not meeting criteria for CR, PR, CI, or PD
Progressive Disease (PD)	• For patients with baseline grade 2 non-hematologic organ damage: a) worsening by 1 grade, AND b) minimum 100% increase (doubling) of laboratory abnormality • For patients with baseline ≥ grade 2 hypoalbuminemia: worsening by 1 grade, AND decrease by ≥ 0.5 g/dL. • For patients with baseline ≥ grade 3 non-hematologic organ damage: minimum 100% increase of laboratory abnormality • For patients with baseline ≥ grade 2 transfusion-independent anemia or thrombocytopenia: New transfusion dependence of ≥ 4 units of red blood cells or platelets at 8 weeks • For patients with baseline transfusion-dependent anemia or thrombocytopenia: ≥100% increase in the average transfusion frequency for an 8 week period compared with the 12 week pretreatment period • For patients with baseline grade ≥ grade 3 neutropenia: > 50% decrease in neutrophil count, AND absolute decrease of neutrophil count of ≥ 250/mm3, AND grade 4 neutropenia OR
Response duration must be ≥ 8 weeks	• Development of at least 10-cm palpable symptomatic splenomegaly for a baseline spleen size of not palpable or ≤ 5 cm, OR if baseline symptomatic splenomegaly is > 5 cm, a > 50% worsening and development of at least 10 cm of palpable symptomatic splenomegaly compared with the baseline value
Loss of Response (LOR)	• Loss of a documented CR, PR, or CI that must be for ≥8 weeks (downgrading of CR to PR or PR to CI is considered as such but is not considered as loss of response unless CI is also lost for a minimum of 8 weeks)

was 24.1 months. Patients with ASM exhibited the highest response rate – 75%, compared to 58% in those patients with SM-AHN and 50% in patients with MCL, and responders to midostaurin demonstrated a significantly increased overall survival compared to non-responders (44.4 months vs. 15.4 months, p = 0.005). The most common adverse events were related to GI toxicity, with 79% of patients reporting nausea, 66% reporting vomiting, and 54% reporting diarrhea. The most frequent reasons for drug discontinuation were progression of disease and adverse events, although no grade III or IV non-hematologic adverse events (most commonly fatigue and diarrhea) were reported at ≥ 10% incidence.

Transplant offers the possibility of cure in patients with ASM. A review of 57 patients with SM treated with alloSCT included 7 patients with ASM, who demonstrated a 3-year OS and progression-free survival (PFS) of 43% [86]. A 2016 consensus statement on alloSCT in SM cited the decreased life expectancy of patients with ASM in their recommendation for the consideration of alloSCT in this setting [92]. Retrospective data indicates an improved survival for patients treated with myeloablative conditioning over reduced-intensity conditioning prior to transplant [69,93]. Debulking prior to alloSCT is recommended to reduce MC burden, although no debulking regimen is considered standard-of-care in this setting – prospective options include cladribine, poly-chemotherapy or investigational agents.

5.5. MCL

MCL is an exceedingly rare disease, accounting for less than 1% of all mastocytosis cases [23]. The median survival of patients with MCL is typically less than a year, and may be lower when an AHN is present [94,95]. The management of MCL differs between chronic MCL (cMCL) and acute MCL (aMCL). cMCL, defined by a BM MC burden > 20% without associated C-findings, has an indolent course similar to ISM/SSM, and patients may have a relatively stable clinical course [96]. These patients may be treated either with 2-CdA or appropriate TKI therapy (imatinib for KIT^{D816V}-negative disease and midostaurin for KIT^{D816V}-positive) and monitored regularly for transformation to aMCL [97].

Patients with aMCL who are candidates for alloSCT are recommended to proceed with transplant as first-line therapy per a recent consensus statement, although outcomes in this setting have been varied [92]. Earlier case reports of patients with MCL treated with alloSCT had largely failed to demonstrate sustained remission [93,98]. A more recent case series described alloSCT in 12 patients with MCL with fair outcomes – transplant related mortality in this series was 33% with an OS of 17% at 3 years [86]. Midostaurin may be an effective treatment for MCL in patients who do not want to pursue, or who are not candidates for, alloSCT. In the trial that led to the approval for midostaurin, 12 patients with MCL exhibited an ORR of 50% and had a median OS of 9.4 months [79]. A recently published 10-year median follow-up of midostaurin for advanced SM included 6 patients with MCL and reported an ORR of 67%, albeit with a median OS of 18.5 months [99]. Polychemotherapeutic regimens may be administered in an attempt to debulk disease, though clinical trials investigating the efficacy of any one regimen are lacking. Hydroxyurea may be used for palliative cytoreduction in patients who are unable to tolerate other therapies [30].

6. Future modalities

The elucidation of molecular drivers and potential therapeutic targets, along with the recent FDA approval for midostaurin in advanced SM, have resulted in a substantial amount of research on novel therapeutic modalities in this disease. When appropriate, patients with SM, especially those with advanced SM, should be referred to appropriate clinical trials given the paucity of treatment options currently available.

6.1. Crenolanib

Crenolanib is a multi-targeted TKI with specificity for both FLT3 and PDGFRα/β. The FLT3 target for crenolanib is homologous to codon 816

in the *KIT* gene, and studies have demonstrated significant affinity for the KIT^{D816V} *ex vivo* that results in an inhibition of cellular proliferation and initiation of apoptosis in mast cell lines [100,101]. Notably, crenolanib demonstrates a much lower affinity for the wild-type KIT, which may translate to a more tolerable side-effect profile versus currently available TKIs. Cortes et al recently published data demonstrating clinical efficacy of crenolanib for patients with relapsed or refractory AML harboring a *FLT3* mutation [102].

6.2. Avapritinib

Avapritinib (BLU-285) is a small molecule inhibitor, first identified via a novel chemical library optimized for kinase sensitivity, which targets *KIT* exon 17, which harbors the pathogenic KIT^{D816V} mutation [103]. A recent phase I dose-escalation study involving 32 patients (17 ASM; 9 SM-AHN; 3 MCL; 2 SSM; 1 other), 88% of whom harbored the KIT *D816V* mutation, reported an 83% ORR per modified IWG-MRT-ECNM criteria in patients with advanced SM, as well as a 58% complete response in BM MC burden and > 50% normalization of serum tryptase levels and observable splenomegaly [104]. Notably, no patients dropped out of the study due to adverse effects, and only 1 grade III or IV adverse effect was recorded in multiple patients (neutropenia, 13%). Of note, a phase II study of avapritinib in patients with advanced SM is currently in recruitment.

6.3. DCC-2618

DCC-2618 is a multi-targeted TKI that slows growth and reduces survival of neoplastic MCs *in vitro* [105]. In addition to suppressing the proliferation of MCs, DCC-2618 was found to inhibit IgE-mediated histamine release in basophils and tryptase release in MCs *in vitro*. DCC-2618 has demonstrated efficacy and safety in phase I trials involving patients with solid tumors, primarily GIST that harbor *KIT* mutations [106]. A phase I study for DCC-2618 in patients with GIST, ASM and advanced malignancies is currently in recruitment.

6.4. SL-401

SL-401 is a targeted therapy directed at the interleukin-3 receptor (CD123) and fused with a diphtheria toxin protein, which is overexpressed in many hematologic malignancies, notably MPNs, AML and MDS [107]. A phase I/II trial that investigated the use of SL-401 for patients with leukemia and MDS has currently completed. Conflicting data regarding CD123 expression on MCs from patients with SM has slowed the progress of investigation of this novel therapeutic target in SM [108].

6.5. Brentuximab vedotin

CD30 expression is aberrantly increased in many patients with SM [109]. Brentuximab vedotin, an anti-CD30 antibody/microtubule disrupter conjugate, has demonstrated clinical activity in patients with ISM and ASM [110,111]. A study of brentuximab vedotin in 10 patients with ASM or MCL was completed in December 2017, though results from the study have yet to be published.

6.6. Bortezomib

SETD2, which encodes a histone methyltransferase gene, has been demonstrated to be universally mutated in SM [112]. Martinelli, et al demonstrated that proteasome inhibition rescued *SETD2* expression and that bortezomib, alone and in combination with midostaurin, reduced growth and induced apoptosis of primary neoplastic MCs *in vitro*. No clinical studies investigating the use of bortezomib or proteasome inhibitors in SM are currently ongoing.

6.7. Other investigational agents

Sunitinib is a multi-targeted TKI that has been demonstrated to be effective in a case of MC activation syndrome, but was intolerable after eliciting a partial response in a patient with ASM [113,114]. Data demonstrating the expression of PD-L1 in SM suggests a possible role for immunotherapy in these patients [115]. Ruxolitinib, a JAK1/2 inhibitor approved for use in other MPNs, has demonstrated efficacy in inhibiting MC degranulation and reducing symptom burden in a patient with ASM [116,117]. Currently, clinical trials investigating agents for all subtypes of SM are in various stages of completion. Some agents under investigation are everolimus (an mTOR inhibitor), thalidomide (an immunomodulatory drug) and tanespimycin (an Hsp90 inhibitor), among others. Future investigational therapies will be developed as our knowledge and understanding of SM continues to increase.

7. Conclusion

SM is a relatively newly described disease entity, having only been officially classified by the WHO after the turn of the 21st century, despite reports of MC related disease dating back to the mid-1800s. The clinical novelty of SM, in addition to its low prevalence and nonspecific manifestations, has made it difficult to conduct meaningful studies in order to evaluate effective therapeutic modalities. Increased recognition of this MPN has been coupled to an increase in the biologic understanding and the translation-of-mechanism-based targeted therapies. The recent approval of the KIT inhibitor, midostaurin, has led the way for the development of other selective kinase inhibitors targeting this disease-associated signaling pathway as well as agents exploiting other features of MC biology. AlloSCT remains the only therapy that offers curative potential to a subset of eligible patients with SM that have advanced disease. Moving forward, it is imperative that institutions collaborate in the evaluation of agents with preclinical rationale in well-designed studies incorporating relevant laboratory correlates and utilizing consensus response criteria.

Authors' contributions

A.C.: provided the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article, and revised it critically for important intellectual content; J.M.: was responsible for the article critically for important intellectual content and provided the revised the article critically for important intellectual content and gave final approval of the version to be submitted.

Conflict of interest

All authors have no conflict of interest to report.

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