

Treatment of Systemic Mastocytosis

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The heterogeneous nature of systemic mastocytosis requires that treatment options be individualized to each patient's clinical presentation and prognosis. Basic management principles include counseling of the patient and care providers, avoidance of factors triggering mast cell mediator release, treatment of acute and chronic mediator-release symptoms, and cytoreductive therapy in those patients with aggressive forms of disease [1]. Disease classification, symptom progression, and overall prognosis determine to what degree each of these principles is used.

Counseling and education

Patient counseling is the foundation of proper management. Educational material on systemic mastocytosis, guidelines for avoidance of situations or agents that may provoke flushing and/or hypotension, and an action plan for life-threatening hypotensive events should be reviewed with patients and their families. Medical alert bracelets should be made available, and an epinephrine self-injector demonstration should be performed. The patient's primary health care providers should be supplied with premedication instructions for general anesthesia and radiologic studies using contrast media. It should be emphasized to patients and health care providers that acute symptoms merit a complete medical evaluation and should not casually be attributed to mastocytosis. Patients and doctors are encouraged to contact referral centers with experience in the diagnosis and treatment of mastocytosis.

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Avoidance guidelines

A major goal in the management of mastocytosis is the avoidance of known and possible inciting factors (Table 1) [2–9]. Although the exact percentage of patients at risk for significant mast cell mediator release is unknown, it is generally accepted that this risk for systemic hypotension is higher than in the nonmastocytosis population. Opioid analgesics, such as morphine, codeine, and pethidine, are known mast cell degranulators and may produce severe adverse reactions in sensitive individuals [2,3]. Direct mast cell activators, such as dextran or iodinated radiocontrast dyes, should also be avoided when possible [3,4]. If necessary, medications that potentially cause mast cell degranulation may be used with caution after premedication or desensitization. Ideally, a medication that the patient has tolerated in the past would be a first choice. If a new medication or procedure is required, premedication with antihistamines and glucocorticoids should be considered as well as administration of a test dose of the drug in an intensive care unit (ICU) or a monitored setting in case an adverse reaction develops.

Certain medications used in general anesthesia are known to induce mast cell mediator release [10–12]. Predicting the occurrence and severity of adverse reactions is difficult, however, because the exact incidence of complications in general anesthesia in mastocytosis is not known, and there appears to be great variability in patient response. There is also great variability in patient response. This is evidenced by reports of severe reactions, including systemic hypotension, anaphylactoid reactions, coagulopathy, and even death [13–16]. A number of protocols aimed at preventing anesthetic

Table 1
Agents and substances associated with mast cell degranulation^a

Triggers	Examples	Comments
Medications	Aspirin, NSAIDS, thiamine, alcohol, narcotics, amphotericin B, radiographic dyes, and some drugs used in general anesthesia (inductors and muscle relaxants)	Aspirin and other NSAIDS may induce mast cell degranulation in some patients and have proven to be well-tolerated effective therapy in others; if radiographic studies are necessary, premedicate patients with H ₁ and H ₂ antihistamines and glucocorticoids
Venoms	Insect, snake	Stinging insect venom immunotherapy may be recommended; effectiveness varies by patient
Polymers	Dextran, gelatin	
Physical stimuli	Heat, cold, friction, sunlight	
Emotional factors	Stress, anxiety	
Allergens ^b	Foods, inhalants	Any identifiable allergen should be avoided

^a Inciting factors vary greatly from patient to patient. Defined sensitivities should be indicated on a medical alert bracelet.

^b Applicable to those with allergies.

complications have been proposed [2,17]. Administration of β -adrenergic blockers is generally contraindicated for patients with mastocytosis undergoing surgery because they may render an anaphylactic episode less responsive to intravenous epinephrine [3,18]. Other pharmacologic agents that should be avoided if possible include α -adrenergic and cholinergic receptor antagonists [3,18]. Before surgery, a close communication between anesthesiologists, surgeons, and intensivists should be established. Serum tryptase levels should be obtained [19], and blood coagulation parameters should be monitored during surgery and anesthesia if a suspected mast cell degranulation event occurs.

Patients with mastocytosis are at increased risk for fatal adverse outcomes after an insect sting, even when adequate desensitization has been demonstrated [6]. Patients, particularly those with known insect hypersensitivity, should exercise great care to avoid stinging insects and to carry epinephrine-filled syringes at all times and be skilled in self-administration [6,20]. Venom desensitization may be considered but is itself not without risk [20].

Management of mediator-release symptoms

Central to the management of all categories of systemic mastocytosis is control of mast cell mediator-induced symptoms [21,22]. These symptoms vary from mild to severe or even life-threatening [1,23,24]. Because of the relatively benign nature of indolent systemic mastocytosis (ISM), symptom amelioration is the main approach to treating this disease variant. A summary of mast cell mediator-related symptoms and recommended medical management is provided (Table 2).

Antihistamines

Histamine is a principal mediator released from mast cells that has profound effects on smooth muscle (contraction), endothelial cells, nerve endings, and mucous secretion [25]. These effects are conducted via H_1 , H_2 , and H_3 receptors. Inhibition of these receptors has been a principle of treatment for most patients with mastocytosis, although total relief of symptoms is rarely achieved. Classic H_1 antihistamines, such as diphenhydramine and hydroxyzine as well as doxepin and ketotifen, have been shown to be useful in mitigating flushing, pruritus, tachycardia, and, in some cases, gastrointestinal cramping [4,22,26–29]. Sedation is frequently a dose-limiting side effect, and although no double-blind placebo-controlled trials have been conducted to assess the relative efficacy of the nonsedating antihistamines (eg, loratadine, fexofenadine, cetirizine), these drugs are often substituted. A combined approach incorporating the use of a nonsedating antihistamine during the day coupled with a sedating antihistamine at bedtime may prove beneficial.

If symptoms persist despite an H_1 antihistamine, some studies have suggested that addition of an H_2 antihistamine, such as ranitidine, cimetidine,

Table 2
Management of mast cell mediator-related symptoms

System	Symptom	Management
Skin	Pruritus	H ₁ and H ₂ antihistamines
	Urticaria pigmentosa	Consider topical corticosteroids Consider PUVA for refractory symptoms
Cardiovascular	Hypotension	Intramuscular epinephrine
	Anaphylaxis	For attempted prophylaxis in patients with frequent life-threatening episodes, consider scheduled H ₁ and H ₂ antihistamines ± glucocorticoids
Gastrointestinal	Abdominal cramping	H ₂ antihistamines ± Leukotriene antagonists
	Peptic ulcer disease	H ₂ antihistamines
	GERD	± Proton pump inhibitor
	Diarrhea	Proton pump inhibitor ± Leukotriene antagonist ± Anticholinergics
	Malabsorption	Cromolyn sodium Consider glucocorticoids
	Ascites	Glucocorticoids Consider portocaval shunt
		Consider cladribine or interferon-α
Musculoskeletal	Osteopenia	Calcium and vitamin D supplementation
	Osteoporosis	Bisphosphonates Consider cladribine or interferon-α in severe osteoporosis
	Bone pain	ASA and other NSAIDS or opioid if tolerated Radiation therapy for severe localized bone pain

Abbreviations: ASA, acetylsalicylic acid; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; PUVA, methoxypsoralen UVA.

or famotidine, may provide additional relief of pruritus and wheal formation [30–33]. H₂ antihistamines are specifically used to treat gastric hypersecretion and peptic ulcer disease associated with mastocytosis [34–37]. Dosages should be adjusted to obtain the most safe and effective regimen for each patient. H₂ antihistamines seem to have a limited effect on gastrointestinal symptoms, such as diarrhea and malabsorption [35,38]. A proton pump inhibitor, such as omeprazole, may decrease diarrhea in addition to controlling gastric acid hypersecretion [1]. Anticholinergics may also be useful in controlling diarrhea [39].

Disodium cromolyn

Oral cromolyn is most frequently administered for diarrhea, nausea, vomiting, and abdominal cramping [40–42]. Because of its limited intestinal absorption, several weeks of therapy may be required before the clinical benefits are observed [43]. The recommended adult dosage is 200 mg administered four times per day, and in children, doses ranging from 60 to 100 mg

administered four times per day have been used [44–47]. Additional studies have suggested that cromolyn may decrease bone pain associated with osteosclerosis, provide headache relief, improve cognitive abilities, and decrease pruritus in some patients [40,48–50].

Glucocorticoids

Malabsorption, hepatic fibrosis, and ascites are known complications of severe mastocytosis [51]. Glucocorticoids are most helpful in managing this cohort of patients. In adults, improvement has been reported with the daily administration of oral prednisone (40–60 mg/d) for 2 to 3 weeks. After initial improvement, tapering to a maintenance dose of 15 to 20 mg every other day is sometimes achievable [29,52,53]. A subgroup of patients with mastocytosis who develop ascites may also develop portal hypertension. In addition to being exceedingly difficult to manage, portal hypertension indicates a poor prognosis. Successful management of at least one patient with portal hypertension was achieved with portacaval shunt placement [54,55].

Glucocorticoids have also proven beneficial in treating the skin symptoms of mastocytosis. It is known that corticosteroids decrease tissue mast cell numbers by reducing the production of stem cell factor by resident cells in the skin [56]. Urticaria pigmentosa responds well to intralesional and topical steroids (0.05% betamethasone dipropionate ointment under occlusion for 8 hours a day over 8–12 weeks). Six months of near-complete remission has been reported with 6 weeks of topical steroid use. Lesions eventually recur after discontinuation of therapy, however [57–59].

Bisphosphonates

Bone marrow infiltration by mast cells may result in osteoporosis, osteopenia, or lytic bone lesions. Therefore, it is not surprising that approximately 25% of patients with mastocytosis may experience some degree of musculoskeletal pain [60]. These clinical sequelae seem to be caused by the release of numerous mast cell mediators that have a direct or indirect effect on bone cells (eg, histamine, heparin, arylsulfatase, tryptase) or are involved in the promotion of the inflammatory response (eg, histamine, heparin, leukotrienes, cytokines) [61]. Osteopenia and osteoporosis treatment should include the selective use of bisphosphonates in conjunction with calcium and vitamin D supplementation [61,62]. Although traditional pain relievers, such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs), may be effective in relieving bone pain, caution should be used in ensuring that the patient is not aspirin sensitive. Narcotic analgesics may be used but also with care, because they may induce mast cell degranulation in occasional patients. Osteoporosis-related bone pain that is refractory to analgesics in patients with advanced ISM and more aggressive forms of mastocytosis may require cytoreductive or radiation therapy [60,63].

UV light irradiation

The oral administration of methoxypsoralen plus UVA (PUVA) radiation has been used to treat the cutaneous symptoms of mastocytosis [64–71]. PUVA radiation therapy seems to relieve pruritus and wheal formation via a transient reduction in cutaneous mast cells or a decrease in mast cell mediator release [47,68,69,71]. Prolonged symptomatic control may occur after a single course of therapy, but 1 to 2 months of therapy are generally required. Disappearance or fading of lesions may last for 6 months to 1 year, but lesions often return within 3 to 6 months after discontinuation of treatment [4,29,72]. A retrospective study of 20 patients found long-term improvement in 25% of patients for more than 5 years [65]. Although cataracts and skin cancers have been reported in patients receiving photochemotherapy, the incidence of these seems to increase with long-term exposure [73]. One study reported that medium-dose UVA1 radiation (60 J/cm²/d for 15 days) was at least as effective as high-dose UVA1 radiation (130 J/cm²/d for 10 days) in decreasing objective and subjective symptoms of adult patients with urticaria pigmentosa [74]. Some patients with mastocytosis report a decrease in the number or intensity of cutaneous lesions after repeated exposure to natural sunlight [72].

Epinephrine

Life-threatening hypotension may occur in all categories of mastocytosis, and patients should be prepared to self-administer intramuscular epinephrine [75–79]. An initial dose of 0.3 mL at a 1:1000 dilution should be used in adults, and an initial dose of 0.01 mL/kg at a 1:1000 dilution should be used in children (up to 0.3 mL). If necessary, this may be repeated every 10 to 15 minutes while en route to the emergency room. Refractory hypotension may require fluid resuscitative measures and additional pharmacologic interventions, such as intravenous dopamine or dobutamine. Once stabilized, the patient should be observed in an ICU environment for at least 24 hours to monitor for a delayed anaphylactic event. To prevent this response, the addition of H₁ and H₂ antihistamines along with glucocorticoids is recommended [22,26,80].

Aspirin and nonsteroidal anti-inflammatory drugs

Mast cell degranulation is a known side effect of NSAIDs in sensitive patients. Despite this, aspirin has been used prophylactically to treat flushing associated with elevated prostaglandin levels during attacks [81,82]. Although mastocytosis-related gastrointestinal bleeding is relatively uncommon, the gastric intolerance and platelet inhibition of aspirin must be considered. Initiation of aspirin treatment should be performed in a hospital setting using prophylaxis with H₁ and H₂ blockers [23,29]. Alternative NSAIDs, such as ibuprofen, are often better tolerated than aspirin and

may also be effective. Ketorolac, a potent NSAID, is generally considered contraindicated, however.

Leukotriene antagonists

No blind, randomized, controlled studies have examined the role of leukotriene antagonists in mastocytosis. Anecdotal reports suggest a transient response to leukotriene antagonists used to treat recalcitrant symptoms. Symptomatic relief has been observed within the first month of treatment but tends to wane thereafter [22].

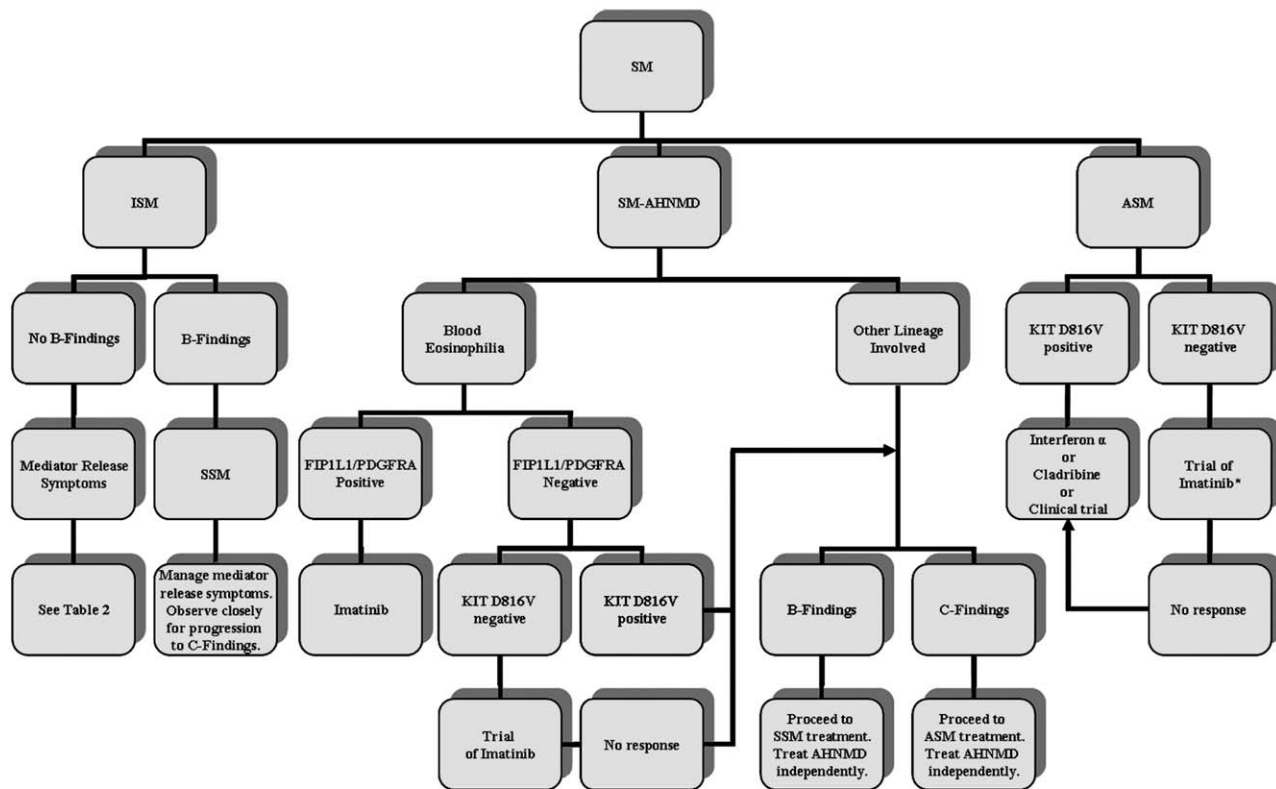
Cytoreductive treatment

Most cytoreductive agents are intrinsically mutagenic, and their use in “low-grade” hematopoietic diseases must be carefully restricted so as to avoid disease progression and development of secondary leukemias [83]. Therefore, these agents are commonly accepted to be contraindicated in most patients with ISM. Patients with smoldering systemic mastocytosis (SSM; B-findings) may be an exception and should be observed closely. Cytoreductive therapy could be initiated, for instance, if there is a rapid progression of the B-findings or new C-findings. C-findings indicate aggressive systemic mastocytosis (ASM) but may also occur in systemic mastocytosis with associated clonal hematologic non-mast-cell lineage disease (SM-AHNMD) or mast cell leukemia (MCL). When C-findings arise, a precise diagnosis is imperative so as to implement the appropriate therapeutic regimen (Fig. 1) [1,84,85]. From a treatment perspective, it is important to note that a diagnosis of SM-AHNMD is considered to represent two separate hematologic disorders and that each should be approached independently. A complete review of disease classification can be found elsewhere in this issue.

Interferon- α

Interferons are a large family of secretory glycoproteins that are known to have immunomodulatory and antiproliferative effects on cells [86]. Interferon- α (IFN α) is the primary interferon produced by leukocytes and consists of at least 14 glycoproteins encoded by a closely related family of genes. It is a nonleukemogenic cytotoxic agent that has demonstrated efficacy in certain myeloproliferative disorders, including chronic myelogenous leukemia [87–90].

IFN α was first reported to show efficacy in a patient with aggressive mastocytosis [91]. Subsequent studies using IFN α , often in combination with glucocorticoids, have reported only variable success [83,91–101]. In one study, a modest reduction in bone marrow infiltration by mast cells was observed [93]; yet, in others, it remained unchanged [101,102]. Serum tryptase levels, a reflection of mast cell burden, were found to be unchanged



**Prior to initiating therapy , ex vivo inhibition assays using patients cells should be performed to assess therapeutic efficacy.*

Fig. 1. Systemic mastocytosis (SM) treatment algorithm.

or increased during IFN α treatment [101,102]. Many patients do report symptomatic benefits, such as control of pruritus, flushing, diarrhea, and abdominal pain [93,103]. Increased bone remineralization and resolution of ascites are also reported [92,100].

Based on these considerations, IFN α is not generally recommended for patients with ISM unless there are severe side effects of osteoporosis, such as collapse of vertebral bodies. If this is the case, consideration may be given to administer low-dose IFN α (3 million IU/wk) without glucocorticoids. Initiation of IFN α should be considered in rapidly progressing SSM, SM-AHNMD (with C-findings), and ASM. A proposed approach includes premedication with prednisolone (50–75 mg administered orally daily) for 3 days, followed by the addition of IFN α at a starting dose of 3 to 5 million IU administered subcutaneously 3 times a week. After a few weeks, the IFN α is increased to 3 to 5 million IU/d and the prednisolone is tapered to as low a dose as possible. Treatment may be continued until there are significant signs of toxicity or no response is observed [83]. Even with the addition of corticosteroids, the use of IFN α is often limited by its formidable side effects, which include fever, myalgias, bone pain, anorexia, depression, fatigue, hypothyroidism, and cytopenias [104].

2-Chlorodeoxyadenosine (cladribine or 2-CDA)

2-Chlorodeoxyadenosine (cladribine or 2-CDA) is a purine nucleoside analogue that undergoes phosphorylation by deoxycytidine kinase and accumulates in the cell as 2-chlorodeoxyadenosine 5'triphosphate [105]. This molecule disrupts DNA synthesis in actively dividing lymphocytes and DNA repair in resting lymphocytes. 2-CDA is approved by the US Food and Drug Administration (FDA) for the treatment of hairy cell leukemia, but it is also reported to be effective in chronic lymphocytic leukemia, non-Hodgkin's lymphoma (NHL), Waldenstrom macroglobulinemia, cutaneous T-cell lymphoma, acute myeloblastic leukemia (AML), and chronic myeloblastic leukemia (CML).

The rationale for its use in mastocytosis is based on its potent activity against monocytes [106], which share a common progenitor with mast cells [107]. 2-CDA's efficacy was initially evaluated in a patient with IFN α -resistant systemic mastocytosis [108]. After four cycles of treatment with 2-CDA, skin lesions resolved and there was a marked reduction in bone marrow mast cell numbers. At one year of follow-up, the patient remained free of clinical symptoms and had near-complete bone marrow histologic remission. Subsequent case reports support 2-CDA's therapeutic potential by demonstrating clinical remissions in patients with more aggressive forms of mastocytosis [109–111]. More recently, 2-CDA arrested progression of MCL for 30 months after diagnosis [112].

Dosing is generally 0.1 to 0.14 mg/kg/d in a 2-hour intravenous infusion for 5 days, which is repeated every 4 to 6 weeks. Prophylactic

glucocorticoids, antihistamines, and antibiotics are recommended. Side effects are related mainly to bone marrow suppression, which may result in pancytopenia and potential opportunistic infections [110]. Although more extensive clinical studies are required, 2-CDA seems to offer a reasonable therapeutic approach in treating patients with aggressive forms (C-findings) of mastocytosis who have IFN α -resistant disease.

Imatinib (STI571, Gleevec)

Imatinib is an ATP-competitive kinase inhibitor of *c-kit*, *c-abl*, *bcr-abl*, and platelet-derived growth factor receptor [113]. It has proven effective in treating the chronic phase of chronic myelogenous leukemia, myeloproliferative hypereosinophilic syndrome (MP-HES), and a subset of gastrointestinal stromal tumors (GISTs) [113–118]. Imatinib's utility in systemic mastocytosis is limited by the nature of the *c-kit* mutation at codon 816, if present. In vitro studies have demonstrated that cell lines carrying the most common *c-kit* mutation found in mastocytosis (D816V) are resistant to imatinib [119–122]. Indeed, this is suggested clinically [123]. In one study, 5 of the 12 patients with systemic mastocytosis who displayed a histologic or clinical response with imatinib lacked a codon 816 mutation [124]. Three of these responders had peripheral blood eosinophilia and were subsequently found to possess the FIP1-like 1/platelet derived growth factor receptor-alpha (FIP1L1/PDGFR α) fusion gene that conferred imatinib sensitivity [125]. Imatinib has also been reported to decrease the bone marrow mast cell burden, serum tryptase level, and clinical symptoms in a patient with a novel mutation (F522C) located in the transmembrane region of KIT [126]. In summary, a trial of imatinib should be considered in patients with ASM who lack the D816V mutation or who have eosinophilia with a positive FIP1L1/PDGFR α fusion gene. The doses used in clinical trials range from 100 to 400 mg/d.

“Traditional” chemotherapies

A variety of “traditional” chemotherapies have been used in an attempt to control symptoms and disease progression in ASM, SM-AHNMD, and MCL (as reviewed by Worobec [22]). These include cytosine arabinoside (ARA-C), doxorubicin, daunorubicin, and vincristine used alone or in combination [22,83,127]. Most studies with these agents are characterized by low patient numbers with short follow-up periods. In general, only partial or short-lived remissions were obtained, and the clinical response most often depended on the prognosis of the underlying disease. Presently, these chemotherapeutic regimens are not considered first-line treatments for aggressive forms of mastocytosis and should only be considered if more promising cytoreductive agents (eg, IFN α , 2-CDA) have failed.

Splenectomy

Palpable splenomegaly with hypersplenism constitutes a C-finding indicative of aggressive disease [128]. Splenectomy has provided benefit in the management of some patients by decreasing mast cell burden and improving cytopenias [129–131]. As a result, this procedure may facilitate the possible use of myelosuppressive agents. Postsplenectomy survival has been reported to increase by an average of 12 months [129]. Nevertheless, splenectomy in patients with aggressive forms of mastocytosis is considered a high-risk operation. Often, these patients have abnormal coagulation test results because of impaired liver function, increasing the risk of bleeding during surgery. In addition, life-threatening anaphylaxis secondary to the massive release of mediators during surgery is always of concern. These risks and benefits should be discussed at length with the patient, allowing for an informed decision to be reached.

Bone marrow transplantation

Experience with bone marrow transplantation in systemic mastocytosis is limited. Traditionally, it has been reserved for patients with advanced and potentially fatal forms of SM-AHNMD and ASM. Favorable engraftment and prolongation of life are reported; however, poor outcomes, including graft-versus-host disease and death, have also occurred [132–135]. Nonmyeloablative bone marrow transplantation has been proven to cause less transplant-related mortality compared with myeloablative transplantation. This approach is designed to take advantage of the graft-versus-tumor effect for further reduction of malignant cells [136–139]. Unfortunately, a recent publication describing this approach in three patients with advanced SM reported no effect on mastocytosis progression, despite inducing a graft-versus-mast cell state [140]. It is speculated that effective cytoreductive therapy before transplantation may be necessary to achieve long-term disease control and cure.

Future therapeutics

The lack of a curative treatment for mastocytosis has driven the pursuit of novel therapeutics. Small-molecular-weight inhibitors targeting the constitutive kinase activity of KIT have become a major focus of clinical development. As discussed previously, imatinib is not effective in treating most patients with mastocytosis because they harbor the resistant D816V KIT mutation. Newly developed tyrosine kinase inhibitors show promise in overcoming this obstacle. A comprehensive review on new drugs targeting KIT as potential therapies for mast cell disease is provided by Gotlib elsewhere in this issue.

PKC412 is a novel staurosporine-derived tyrosine kinase inhibitor that has displayed potent activity (50% inhibitory concentration [IC₅₀] of 30–40 nM) against KIT 816 mutants in vitro [141]. Using the murine hematopoietic cell line Ba/F3, transformed with KIT D816V and D615Y, PKC412 proved to inhibit autophosphorylation of KIT and activation of downstream effectors Stat5 and Stat3 [141]. Clinically, the efficacy of PKC412 has been assessed in a patient with MCL with an associated myelodysplastic/myeloproliferative disorder [142]. The patient exhibited a partial response with significant resolution of liver function abnormalities accompanied by a decrease in peripheral mast cells, serum histamine levels, KIT phosphorylation, and frequency of cells bearing the D816V KIT mutation. Unfortunately, the patient died after 3 months of therapy as a result of disease progression. This case suggests that the clinical efficacy of PKC412 may be limited by clonal evolution in the advanced leukemic phase of disease. Further studies aimed at assessing the clinical efficacy of this agent in ASM are in progress.

A rational drug design approach led to the development of a structural derivative of imatinib, AMN107, which possesses a 20-fold improved affinity for wild-type Bcr/Abl [143]. AMN107 shows affinity for KIT as well, although its improved binding affinity for Bcr/Abl is not seen with KIT [143]. Despite this, AMN107 decreases growth and induces apoptosis in Ba/F3 cells transformed with the imatinib-resistant D816V KIT mutant [144]. A phase I trial of AMN107 in the treatment of imatinib-resistant CML has shown encouraging results [145], but its clinical efficacy in systemic mastocytosis has yet to be determined.

Dasatinib (BMS-354825) is a novel dual SRC/ABL kinase inhibitor active against multiple imatinib-resistant Bcr/Abl isoforms [146]. It has shown efficacy in a phase I trial of Philadelphia chromosome positive (PH+) patients with CML in the chronic phase with hematologic progression or intolerance to imatinib [147]. In the human mast cell HMC-1.1⁵⁶⁰ and HMC-1.2^{560/816} cell lines carrying activating *c-kit* mutations in the juxtamembrane (560) and tyrosine kinase (816) domains, dasatinib exhibits an IC₅₀ of 4.6 to 7.5 nM for the juxtamembrane mutant (HMC-1.1⁵⁶⁰) and 490 to 1239 nM for the combined juxtamembrane and tyrosine kinase domain mutated cell line (HMC-1.2^{560/816}) [148,149]. Moreover, preferential cytotoxicity to neoplastic mast cells was demonstrated in mononuclear cell cultures established from patients with mastocytosis (KIT D816V) in the presence of dasatinib at a concentration of 0.1 μM, with increased activity observed at 1 μM. In contrast, imatinib had no significant activity at 1 μM. Clinical trials in systemic mastocytosis are presently underway.

MLN518 is yet another tyrosine kinase inhibitor that has been shown to be well tolerated in phase I clinical trials for AML. MLN518 has the ability to inhibit cell proliferation and phosphorylation of KIT and Stat3 in cell lines containing juxtamembrane and kinase domain mutated KIT [150,151]. This inhibitory potency, coupled with minimal toxicity, has made MLN518 a promising candidate in the treatment of systemic mastocytosis.

ATP-based approaches to inhibit tyrosine kinases are also in development. AP23464 and AP23848 are ATP-based 2,6,9-trisubstituted purines proven to inhibit activation loop mutants of KIT while maintaining normal hematopoietic progenitor cell growth. In a murine model, AP23848 inhibited the activation loop mutant KIT phosphorylation as well as tumor growth [152]. No clinical results are reported to date.

Beyond tyrosine kinase inhibitors are experimental compounds with unique targets of mast cell inhibition. 17-Allylamino-17-demethoxygeldanamycin (17-AAG) is a benzoquinoid ansamycin antibiotic that binds to heat shock protein 90 (hsp90) and promotes the degradation of a variety of client proteins important in the proliferation and survival of malignant cells. In cell lines expressing constitutively activated forms of KIT, 17-AAG significantly decreased the level and activity of KIT, resulting in the downregulation of downstream signaling (AKT and Stat3). Further evidence of therapeutic efficacy was suggested when neoplastic mast cells isolated from patients with mastocytosis were selectively sensitive to 17-AAG [153].

Interference of nuclear factor (NF)- κ B signaling might also prove to have therapeutic potential in systemic mastocytosis. IMD-034 is a novel NF- κ B inhibitor that has been shown to restrain factor-independent proliferation of several mast cell lines with kinase domain and juxtamembrane domain KIT mutations but does not affect the growth of normal mast cells [154].

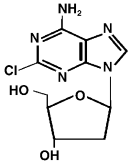
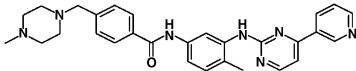
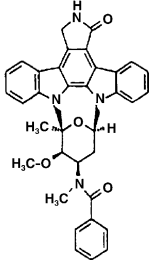
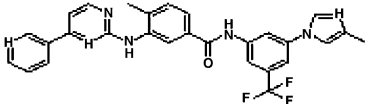
Although the clinical benefit of these newly developed inhibitors requires individual evaluation, a powerful approach in the future may prove to be combination therapy with targeted agents that have different mechanisms of action [143]. Indeed, a recent report using PKC412 in combination with AMN107, imatinib, or cladribine observed synergistic growth inhibition of HMC-1.1 cells (juxtamembrane mutation) and additive effects in HMC-1.2 cells (juxtamembrane and kinase domain mutations) [155]. A summary of prospective clinical and experimental cytoreductive agents is provided (Table 3).

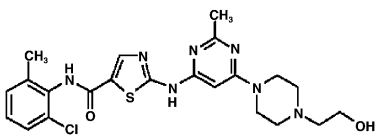
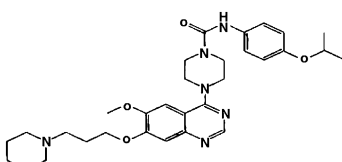
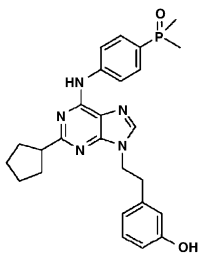
Assessing therapeutic response

Monitoring therapeutic success of cytoreductive agents may use markers reflecting C-findings (eg, elevated liver enzymes, elevated serum calcium, decreased hemoglobin) or those reflecting mast cell burden (serum tryptase levels, bone marrow histology, soluble KIT, and CD25). Given the longevity of the mast cell, C-finding-related parameters may resolve before observing a mast cell decline.

Response criteria using C-finding-related parameters to divide patients into major, partial, or nonresponders have been proposed (Box 1) [83]. A major response is defined by complete dissolution of one or more C-finding(s) and no progression in other C-finding(s). This group is further divided into those with complete remission (disappearance of mast cell infiltrates

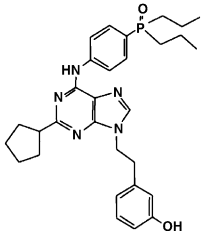
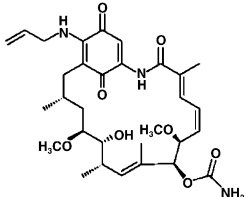
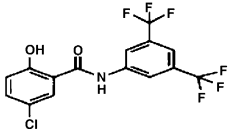
Table 3
Cytoreductive agents in mastocytosis

Name	Structure	Class	KIT D816V Cell proliferation IC ₅₀ (nM) ^a	Reported clinical activity	References
Interferon- α	15–21-kd glycoprotein	Immunomodulator	ND	Yes	[83,91–104,156–158]
Cladribine		Purine nucleoside analogue	ND	Yes	[108–112,159]
Imatinib		Tyrosine kinase inhibitor	> 10,000	Yes	[119–124,126,155,160]
PKC412		Tyrosine kinase inhibitor	30–250	Yes	[141,142,155,161]
AMN107		Tyrosine kinase inhibitor	1000–5000	No ^b	[144]

Dasatinib		Tyrosine kinase inhibitor	490–1239	No ^b	[148,149]
MLN518		Tyrosine kinase inhibitor	250	No	[150]
AP23464		Tyrosine kinase inhibitor	11	No	[152]

(continued on next page)

Table 3 (continued)

Name	Structure	Class	KIT D816V Cell proliferation IC ₅₀ (nM) ^a	Reported clinical activity	References
AP23848		Tyrosine kinase inhibitor	15	No	[152]
17-AAG		Chaperone inhibitor	500	No ^b	[153]
IMD-0354		NF-κB inhibitor	28–35	No	[154]

Abbreviations: IC₅₀, 50% inhibitory concentration; ND, not determined; NF, nuclear factor.

^a Various human cell line systems expressing the KIT D816V mutation were used between studies to derive the IC₅₀.

^b Clinical trial in progress.

Box 1. Proposed response criteria for patients with aggressive systemic mastocytosis

Major response

Complete resolution of at least one (one or more) C-finding(s) and no progression in other C-findings

- (a) Complete remission = with disappearance of mast cell infiltrates in affected organs, decrease of serum tryptase levels to <20 ng/mL, and disappearance of SM-associated organomegaly
- (b) Incomplete remission = with decrease in mast cell infiltrates in affected organs and/or substantial decrease of serum tryptase level and/or visible regression of organomegaly
- (c) Pure clinical response = without decrease in mast cell infiltrates, without decrease in tryptase levels, and without regression of organomegaly

Partial response

Incomplete regression of one or more C-finding(s)^a without complete regression and without progress in other C-findings

- (a) Good partial response: >50% regression
- (b) Minor response: ≤50% regression

No response

C-finding(s) persistent or progressive^b

- (a) Stable disease: C-finding parameters show constant range
- (b) Progressive disease: one or more C-finding(s) show progression

^a With or without decrease in mast cell infiltrates, serum tryptase levels, and organomegaly.

^b In case of progressive C-findings and documented response in other C-finding(s), the final diagnosis is still progressive disease.

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and surrogate markers in follow-up investigations), incomplete remission (incomplete regression of mast cell infiltrates and surrogate markers), or pure clinical response (disappearance of C-findings without change in mast cell infiltrates). Partial responders display measurable improvement in one or more C-findings without progression in other C-findings. Quality of response further divides this group into good partial response (regression

of C-findings to more than 50%) or minor response (regression of C-findings to less than 50%). Nonresponders show no significant response to cytoreductive agents and have stable (stable C-findings) or progressive disease (one or more progressive C-findings). As more promising therapeutics become available, well-defined response criteria should aid in defining clinical efficacy.

Summary

It is an exciting time in the treatment of systemic mastocytosis. Major advances in the past 2 decades have helped to define the molecular abnormalities associated with this disease and to delineate pathways involved in its pathogenesis. This has directly translated into the development of novel targeted therapies. These therapies hold great promise to patients and health care providers that a "cure" for systemic mastocytosis may someday be obtainable.

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