Mastocytosis

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KEYWORDS

• Masocytosis • Update • Review • Pathophysiology • Diagnosis • Treatment
• Cutaneous mastocytosis • Systemic mastocytosis

KEY POINTS

- Mastocytosis is a rare disease, characterized by excessive production of mast cells that accumulate in the skin, bone marrow, and other visceral organs.
- The prevalence of mastocytosis is estimated to be 1 in 60,000 in the United States; children tend to have benign forms of mastocytosis, whereas adults may develop aggressive disease.
- The most common mutation is in the C-kit gene, which causes increased proliferation of mast cells; other causes exist but are less frequent.
- Clinical presentation of mastocytosis is variable, often based on the type of mastocytosis, but in all types of mastocytosis there seems to be an increase in the risk of anaphylaxis; patients may present with skin lesions, flushing, diarrhea, lymphadenopathy, hepatosplenomegaly, osteoporosis, and recurrent anaphylaxis.
- For systemic mastocytosis (SM), the preferred method of diagnosing is via bone marrow biopsy.

INTRODUCTION

Mastocytosis is a rare disease, characterized by excessive production of mast cells that accumulate in the skin, bone marrow, and other visceral organs.[1] In a majority of cases, the disorder is due to a nonhereditary somatic mutation in the KIT gene, which leads to heightened proliferation and activation of morphologically and clinically abnormal mast cells.[2] Mast cell activation results in release of mediators by degranulation, and synthesis of lipids and proteins.[3] These mediators are responsible for the clinical manifestations, which include pruritus, flushing, diarrhea, headaches, and life-threatening anaphylaxis.[3] The World Health Organization (WHO) has classified mastocytosis into 7 categories. Broadly, it can be divided into cutaneous mastocytosis (CM) and SM. CM is relatively benign and affects the skin whereas SM involves an extracutaneous organ and has aggressive potential.[4] The most common form of CM is urticarial pigmentosa.[5] SM is subclassified into indolent SM (ISM), associated

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clonal hematologic non–mast cell lineage disease (AHNMD), aggressive SM (ASM), and mast cell leukemia (MCL) (Table 1).

EPIDEMIOLOGY

The prevalence of mastocytosis is estimated to be 1 in 60,000 in the United States. The disease occurs in both children and adults. Children tend to have benign forms of mastocytosis, whereas adults may develop aggressive disease. The true number of cases of mastocytosis is unknown.[1] Its prevalence is estimated to be 1 in 60,000 and incidence 0.5 to 1 per 100,000 per year in the United States.[6] Mastocytosis is a disease of both children and adults, with equal male and female prevalence.[7] A majority of patients are children and are typically affected by CM forms, which carry an excellent prognosis.[8] In many children, symptoms regress spontaneously by puberty.[8] Adults are much more likely to have urticarial pigmentosa and ISM. In adults, the onset of mastocytosis is generally at age 20 to 50 and is diagnosed between 40 and 60 years of age.[3,7] The disease is congenital in approximately 15% to 25% of cases and, in these patients, usually occurs before the age of 2.[3,7,9] In a majority of cases, the disease is spontaneous.[3]

MAST CELL BIOLOGY

Mast cells act as effector cells in allergic and hypersensitivity disorders and are activated through IgE and non-IgE mechanisms. Once activated, they release proinflammatory and vasoactive mediators. Mast cells arise from pluripotent cells in the bone marrow, acquire cytoplasmic granules, and mature in specialized tissues.[1,4,7] They act as sentinels of the innate and adaptive immune system and are abundant in endothelial and mucosal surfaces.[2,6,10,11] Mast cells have a central role in immunomodulation and act as effector cells in allergic and hypersensitivity disorders.[12] Activation and degranulation of mast cells occur through IgE and non-IgE receptor cross-linking.[7,10]

Table 1
World health organization classification of mastocytosis

CM	• Urticaria pigmentosa or maculopapular CM • DCM • Mastocytoma of skin

SM	• ISM
	  ○ Isolated bone marrow mastocytosis
	  ○ Smoldering SM
	• SM-AHNMD
	  ○ SM with acute myeloid leukemia
	  ○ SM with myelodysplastic syndrome
	  ○ SM with myeloproliferative disorder
	  ○ SM with chronic myelomonocytic leukemia
	  ○ SM with hypereosinophilic syndrome
	• ASM
	  ○ Lymphopathic SM with eosinophilia
	• MCL
	  ○ Classic
	  ○ Aleukemic MCL

MCS	
Extracutaneous mastocytoma	

Data from Valent P, Akin C, Wolfgang S, et al. Mastocytosis: pathology, genetics and current options for therapy. Leuk Lymphoma 2005;46:35–48.

Non-IgE–mediated activation includes hymenoptera stings, foods, drugs, alcohol, physical and emotional stimuli, heat, cold, exercise, ionizing radiation, complement, hormones, and cytokines.[7,13] Pharmacologic agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and muscle relaxants, cause mast cell mediator release, most notable in skin mast cells.[14] When activated, granules within mast cells release histamine, serotonin, heparin, phospholipases, and proteases (ie, tryptase and chymase), prostaglandins, thromboxanes, cytokines, tumor necrosis factor, and growth factors.[7,10–12] Tryptases and chymases account for the bulk of protein release from mast cell secretory granules.[10] Tryptase is produced almost exclusively by mast cells and, therefore, is used as a biological marker of disease.[14]

PATHOPHYSIOLOGY

The most common mutation is in the C-kit gene, which causes increased proliferation of mast cells. Other causes exist but are less frequent (**Table 2**).

CLINICAL MANIFESTATIONS

Clinical presentation of mastocytosis is variable, often based on the type of mastocytosis, but in all types of mastocytosis there seems to be an increase the risk of anaphylaxis. Patients may present with skin lesions, flushing, diarrhea, lymphadenopathy, hepatosplenomegaly, osteoporosis, and recurrent anaphylaxis.[13] Lung and kidney involvement is rare.[3] The most common symptom is pruritus.

Symptoms often vary based on the type of mastocytosis. The clinical manifestations of the disease may be variable, ranging from asymptomatic disease to systemic involvement.[3,6] This depends the extent of mast cell penetration in tissues.[6] CM is due to limited aggregation of mast cells in skin tissues.[10] For CM, common symptoms are itching, swelling, and blistering of the affected skin, particularly when it is rubbed or scratched, and is sometimes associated with abdominal cramping or anaphylaxis.

SM symptoms may be chronic or episodic.[3] In progressive stages of the disease, mast cell end-organ damage causes weight loss and pathologic fractures and ascites may occur.[3,14] The most common trigger of symptoms in SM is stress.[12] Most patients present with classic skin findings and may be diagnosed with urticarial pigmentosa. The absence of skin findings in SM is rare and is correlated with aggressive disease (**Table 3**).[6]

Table 2
Causes of mastocytosis and pathophysiologic effect

Etiology	Effect
C-kit gene mutation	"Activating" mutation → increased productivity → increase in mast cells numbers and activation (SM)
Other mutations: FIP1L1/PDGFRA, JAK2V617F, RAS, TET2 and IgE receptor genes	SM forms: SM-AHNMD, ASM, and MCL
CD2 cell surface antigen expression	CD2-CD58 interaction → infiltration of mast cell in tissue → release of mediators → organ damage → disease sequelae
Failure of mast cell apoptosis	Increase number of mast cells → release of mediators → organ damage → disease sequelae

Data from Refs.[3,7,9,10,15–17]

Table 3
Clinical manifestations of mastocystosis

Organ System	Symptoms/Findings
Constitutional	Fatigue, lethargy, weight loss, chills, weakness, sweats, fever
Skin	Flushing, pruritus, urticaria, hives, angioedema
Neurologic/ psychological	Headaches, trouble concentrating, dizziness, depression, anxiety, sleep disturbances
Respiratory	Anaphylaxis, shortness of breath, wheezing, nasal congestion, nasal pruritus
Cardiovascular	Hypotension, palpitations, tachycardia, syncopal episodes, light-headedness, pericardial effusions
GI	Diarrhea, nausea, vomiting, abdominal pain, bloating, heartburn, peptic ulcers, gastritis, hepatosplenomegaly, hypersplenism
Musculoskeletal	Myalgias, arthralgias, osteoporosis, pathologic fractures
Reproductive	Uterine cramping
Hematopoietic	Lymphadenopathy, bleeding disorders, cytopenia, recurrent infections

Data from Refs.[3,5–7,10,12–14,17–22]

DIAGNOSIS

Overview of Diagnostic Tests

The following tests may be useful as part of a mastocytosis diagnostic evaluation.

Bone marrow biopsy

Bone marrow biopsy is performed to make a diagnosis of systemic mastocystosis, as discussed later.

Skin biopsy

A skin biopsy is crucial to confirm a diagnosis of CM.[5]

Total tryptase level

Tryptase is a marker of mast cell degranulation released in parallel with histamine and is typically elevated in those with SM.[23,24] Patients with CM often have normal levels of total tryptase. In children with CM, however, elevated serum baseline tryptase may predict an increased risk of anaphylaxis. One study found that children with tryptase levels greater than 6 ng/mL are more likely to require daily treatment to manage symptoms and prevent severe episodes, and those with levels greater than 15.5 ng/mL were at risk for hospitalization.[25] The total tryptase level in serum or plasma seems to be a more discriminating biomarker than urinary methylhistamine for a diagnosis of SM.[26] As discussed previously, total tryptase values are recommended by the WHO as a minor criterion for use in the diagnostic evaluation of SM.

Complete blood cell count with differential

In SM, complete blood cell counts may reveal anemia, thrombocytopenia, thrombocytosis, leukocytosis, and eosinophilia as well as abnormal forms, because advanced forms of SM can be associated with other hematologic malignancies.[9]

Blood smear

A blood smear can be done to evaluate for possible associated hematologic malignancies.

Plasma or urinary histamine level
Although not routinely ordered, patients with mastocytosis often have elevated 24-hour urine histamine levels. Compared with total tryptase level, urine or plasma histamine seems a less specific biomarker for the diagnosis of SM.[26]

Serum chemistry panel
Serum chemistry panel with SM is used to monitor for liver involvement and electrolyte imbalances.

Regular bone densitometry
Regular bone densitometry for patients with SM is used to screen for and monitor osteopenia or osteoporosis.

Abdominal ultrasound
Abdominal ultrasound can be useful to evaluate for organomegaly with SM.[5]

Diagnosis of Systemic Mastocytosis

For SM, the preferred method of diagnosing is via bone marrow biopsy. The WHO has established the following criteria for diagnosing SM.[9,27]

Major criterion
Multifocal dense infiltrates of mast cells (>15 in aggregate) in tryptase-stained biopsy sections of the bone marrow or of another extracutaneous organ.

Minor criterion

1. In biopsy of bone marrow or other extracutaneous organ(s), more than 25% of the mast cells show abnormal morphology (ie, are atypical mast cell type I or are spindle shaped) in multifocal lesions in histologic examination.
2. A point mutation at codon 816 in the KIT receptor gene may be detected in bone marrow, blood, or other internal organ.
3. KIT-positive mast cells in bone marrow, blood, or other internal organs are found to express CD2 and/or CD25.
4. Serum total tryptase level persistently is greater than 20 ng/mL. (Note: this criterion cannot be used if a patient has an AHNMD disorder.)

*** The presence of 1 major and 1 minor criteria or 3 minor criteria constitute a diagnosis of SM.

Diagnosis of the different mastocytosis categories
Indolent systemic mastocytosis A majority of adult patients with SM are in the ISM category.[28] These patients fit the criteria for SM and may have an enlarged liver or spleen. The gastrointestinal (GI) tract also may be affected. Mediator-related symptoms are common, but the grade of bone marrow infiltration is low, usually less than 5%.[28] In most patients, the serum tryptase concentration exceeds 20 ng/mL, but a normal level of tryptase does not rule out either mastocytosis or another mast cell activation disorder.[28]

Systemic mastocytosis with associated clonal hematologic non–mast cell lineage disease Patients with SM with AHNMD fit the WHO criteria for SM AND myelodysplastic syndrome, myeloproliferative syndrome, acute myeloid leukemia, or non-Hodgkin lymphoma.[28] These patients often do not have urticaria pigmentosa–like skin lesions.

Agressive systemic mastocytosis In the rare disorder, ASM, patients fit the criteria for SM, and their bone marrow biopsy reveals abnormal blood cell formation that does not fit the diagnostic criteria for myelodysplastic syndrome, myeloproliferative syndrome, acute myeloid leukemia, or non-Hodgkin lymphoma.[28] The prognosis and clinical course of patients with ASM is variable, with some patients experiencing a rapidly declining course over 1 to 2 years, whereas others follow a slower course with several years of survival.[28]

Mast cell leukemia MCL is rare and those with this diagnosis fit the criteria for SM and the presence of greater than or equal to 20% atypical mast cells in the marrow or greater than or equal to 10% in the blood; however, an aleukemic variant is frequently encountered in which the number of circulating mast cells is less than 10%.[29] The shape of mast cells and their nuclei have malignant features. Patients with MCL have an overall poor prognosis. Progression to multiple organ failure with weight loss, bone pain, and organomegaly develops over weeks to months, with death usually occurring within 12 to 24 months of diagnosis.[29,30]

Diagnosis of Cutaneous Mastocytosis

Approximately two-thirds of cases of CM occur in children. CM is diagnosed by the presence of typical skin lesions that demonstrate the Darier sign and a positive skin biopsy demonstrating characteristic clusters of mast cells. A Darier sign is demonstrated when the skin lesion of CM becomes raised and erythematous and itches when it is rubbed briskly. Patients with CM do not fulfill diagnostic criteria for SM (as discussed previously) and show no evidence of organ involvement other than the skin.[24,31] Rarely, CM can present with acute mast cell activation events, including anaphylaxis.

There are 3 types of cutaneous mastocytosis.

1. Urticaria pigmentosa, also known as maculopapular CM, is the most common form of mastocytosis in adults and children, representing 70% to 90% of cases.[5]
2. Diffuse CM (DCM) is rare but can present with more severe symptoms. DCM accounts for 1% to 3% of the cases of CM and can involve the whole skin with the central region and scalp most affected. DCM can appear at birth (congenital and neonatal) or in early infancy. Blistering and bullae may be the presenting symptoms and the blisters can be hemorrhagic.[5]
3. Solitary mastocytoma (mastocytoma of skin) is the second most common form of childhood-onset CM, accounting for approximately 10% to 15% of cases. It often develops before 1 year of age, with most cases presenting within the first 3 months of life; adult involvement is rare.[32]

Other Mastocytosis Diagnostic Categories

Mast cell sarcoma

Mast cell sarcoma (MCS) is a unifocal mast cell tumor with no evidence or criteria for SM and no other skin lesions. There is a destructive growth pattern and high-grade cytology.[33] Systemic involvement is not found among patients at diagnosis of MCS, but generalization with extension to various organs and hematopoietic tissues may occur and even lead to MCL.[9]

Extracutaneous mastocytoma

Extracutaneous mastocytoma is a unifocal mast cell tumor with no evidence or criteria for SM and no other skin lesions. There is a nondestructive growth pattern and low-grade cytology.[9]

MASTOCYTOSIS TREATMENT

Trigger Avoidance

Patients with SM should be counseled that various exposures and situations can trigger symptoms and should avoid exposures that trigger or aggravate their symptoms to the extent possible. These exposures may include heat, humidity, cold, emotional stress, strenuous exercise, alcohol, spicy food, infections, vaccinations, anesthesia, surgery, medications, and endoscopic procedures and lack of sleep. Insect stings can precipitate symptoms in patients with mastocytosis, even when there is no IgE-mediated venom allergy detectable by skin or blood testing. In infants and children, symptoms can be induced or aggravated by mood (anger or irritability), fever, skin abrasion, or rubbing, and teething can induce symptoms.[25] There are various medications that may cause mast cell activation in patients with both CM and SM. Therefore, if possible, the following medications should be avoided: opioids, vancomycin, aspirin and other NSAIDS, radiocontrast agents, thiamine, quinine, and succinylcholine.[34–36]

Anaphylaxis Treatment

The incidence of anaphylaxis is much higher in those with mastocytosis.[18,37] All patients and caretakers should be taught how to recognize and treat anaphylaxis and carry an epinephrine autoinjector. Hymenoptera stings, in particular, are prone to cause anaphylaxis in patients with mastocytosis.[38] All patients with reactions to hymenoptera stings should be evaluated with skin tests or in vitro tests for venom-specific IgE, and those testing positive should be offered venom immunotherapy to reduce the risk of anaphylaxis on subsequent stings. Venom immunotherapy is effective to treat IgE-mediated hymenoptera anaphylaxis in patients with mastocytosis. Its use is recommended despite a high risk of adverse reactions during the build-up phase because it provides protection from anaphylaxis in approximately three-quarters of the patients.[39] The risk:benefit ratio for immunotherapy with hymenoptera venom favors immunotherapy, because patients with mastocytosis can suffer severe anaphylaxis in response to an hymenoptera sting, including fatalities even with epinephrine treatment.[38] Pretreatment with omalizumab may reduce the risk of systemic reactions to venom immunotherapy for those with mastocytosis, but it is not currently approved for this use in the United States.[40]

Mastocytosis patients with recurrent anaphylaxis should be treated with maximized doses of antimediator agents (maximal doses of H_1-antihistamines and H_2-antihistamines and antileukotriene drugs). In patients unresponsive to antimediator therapy, low-dose maintenance glucocorticoids or cytoreductive measures (interferon [IFN] alpha, cladribine, omalizumab, or tyrosine kinase inhibitor, depending on c-kit mutational status) can be considered.[41]

SYMPTOM-SPECIFIC TREATMENT

There is no curative therapy for mastocytosis. Therefore, treatment is intended to reduce the following symptoms and improve quality of life.[42]

See **Table 4** for a list of treatments of cutaneous symptoms.

Treatment of Gastrointestinal Symptoms

Oral cromolyn can help treat GI symptoms, such as diarrhea and abdominal pain, nausea, and vomiting.[45]

Table 4
Treatment of cutaneous symptoms

Medication	Indicated for
Topical steroids or intralesion steroid injections	Topical or intralesional steroids can be used for cutaneous lesions that involve a limited body area. Systemic corticosteroids can be used with severe skin disease.
Psoralen–UV-A photochemotherapy	Cutaneous lesions
H_1-antihistamines	Pruritus, flushing
Leukotriene receptor antagonists (montelukast and zafirlukast)	Flushing, and itching in patients unresponsive to H_1-antihistamines
Oral cromolyn (FDA approved for mastocytosis)	Pruritus, whealing, and flushing
Aspirin (up to 650 mg twice daily)	Helps with flushing, if the patient is known to tolerate NSAIDs

Data from Refs.[43–45]

H_2-antihistamines (cimetidine, ranitidine, and famotidine) and proton pump inhibitors may be used to treat abdominal discomfort and gastroesophageal reflux disease.[9]

Leukotriene receptor antagonists (montelukast and zafirlukast) may help abdominal cramping.[46]

Anticholinergics and menthol can be used to relieve intestinal cramping.

Systemic steroids can be used to help treat malabsorption that can occur with SM.

Treatment of Musculoskeletal Symptoms: Bone Pain, Osteoporosis, and Fractures

Oral cromolyn may help relieve bone pain.

Vitamin D (and calcium) can be supplemented to reduce risk for osteoporosis and fractures.[20]

Spine x-ray and densitometric examinations are recommended to screen for osteoporosis/fractures.

Treatment of Depression

Antidepressants: selective serotonin reuptake inhibitors and tricyclic antidepressants can be used to treat depression in mastocytosis.

Tyrosine kinase therapy may improve depressive symptoms in patients with SM.[47]

Treatment of Lung symptoms

β_2-Agonists can relieve bronchoconstriction that can occur from increased histamine levels.

Inhaled or systemic corticosteroids can treat airway inflammation and associated bronchoconstriction.

Treatment of Ascites

Systemic steroids may be useful in mastocytosis associated ascites.[9] Overall, however, systemic therapy with corticosteroids is often disappointing because the primary mode of action of corticosteroids is redistribution rather than death of mast cells.

Associated Cognitive Disorders

H_1-antihistamines and H_2-antihistamines are considered first-line treatments.[9]

Oral cromolyn is considered second-line treatment of mastocytosis-related cognitive dysfunction.

DIAGNOSIS-SPECIFIC TREATMENT

Treatment of Cutaneous Mastocytosis

There are no therapies that change the natural course of CM and none of the currently available therapeutic measures induces permanent involution of cutaneous or visceral lesions. A few patients with CM may experience a regression of cutaneous lesions without treatment, which can correspond to either improvement or possible progression to systemic disease. Therapy is conservative and aimed at symptom relief because the prognosis for most patients with CM is excellent. The management of CM includes lifestyle modifications, such as the use of lukewarm water for bathing, air conditioning for hot weather, and avoidance of triggers for mast cell degranulation. Patients should be advised to avoid agents that precipitate mediator release, such as NSAIDs, alcohol, and opiates.

Symptomatic therapy for CM involves agents that inhibit the release of mediators or antagonize H_1 and H_2 receptors, such as antihistamines. Skin-targeted therapies aimed at resolution of the lesions of CM are psoralen–UV-A photochemotherapy and topical corticosteroid therapy either by occlusion or intralesional injection for a few lesions.[44] Risks of skin cancer increases, however, with repeated psoralen–UV-A photochemotherapy, if more than 200 treatments are required.[48] H_1-antihistamines and H_2-antihistamines can be used to decrease pruritus, flushing, and GI symptoms. Nifedipine, a calcium channel blocker, may inhibit cold-induced urtication and flushing in patients with CM but is not Food and Drug Administration (FDA) approved for treatment of mastocytosis.[49] Treatment selection is made on the basis of clinical manifestations, onset of disease, probability of spontaneous involution, and severity of CM and SM symptoms.[44] Future novel therapy for CM includes immune modulators, such as imatinib. One successful case report from 2008 described successful treatment of disease symptoms and progression with imatinib.[50]

Treatment of Systemic Mastocytosis

SM has no known cure and tends to be progressive.[42] The treatment algorithm for SM is complex, and the condition is primarily managed by a hematologist. Patients with advanced forms should be referred to centers with expertise in SM. The mainstay of treatment of most categories of mastocytosis is H_1-antihistamines and H_2-antihistamines with the addition of corticosteroids for more severe symptoms. Commonly used H_1-antihistamines include oral cetirizine, fexofenadine, hydroxyzine, or doxepin and commonly used H_2 blockers include ranitidine, cimetidine, and famotidine.[43] Other commonly used treatments for SM include corticosteroids, leukotriene inhibitors, cromolyn, and IFN. Pharmacotherapies may be needed for patients with any subtype of SM, although symptoms arising from mediator release are most prominent in patients with ISM and ASM.

Although most patients have the indolent variant of SM, in which intensive therapy is not needed, others can suffer from serious disease with aggressive behavior requiring mast cell eradication with cytostatic growth-inhibitory drugs.[51] Among these, IFN alfa and cladribine have shown considerable improvement in symptoms, but none of the treated patients achieved a complete remission.[51] Moreover, both drugs are bone marrow suppressive and cause serious side effects.[51]

Tyrosine kinase inhibitors may be appropriate for some patients with SM. Effective suppression of activated c-kit can result in killing of KIT-mutated mast cells and improvement in SM symptoms.[16,52] Tyrosine kinase inhibitors, however, vary in their ability to act on wild-type or mutated molecules. Imatinib is a tyrosine kinase inhibitor approved by the FDA for use in patients with ASM with organ dysfunction due to progressive infiltration of various organs by mast cells without D816V c-*kit* mutation or unknown c-*kit* mutation status.[53] Unfortunately, most patients with SM are not candidates for imatinib (Gleevec) therapy because they have the D816V KIT mutation, which confers resistance to imatinib.[54] Other tyrosine kinase inhibitors that have been administered to patients with SM include masitinib, and dasatinib. Masitinib is a promising treatment of indolent forms of SM,[55] but clinical trials with dasatinib have not yielded significant improvements.[56,57]

Allogeneic hematopoietic cell transplantation has been performed in a few patients with advanced forms of SM but it is not appropriate for indolent or cutaneous forms of mastocytosis.[58] Other possible treatments for SM include calcineurin inhibitors, such as pimecrolimus.[59]

Treatment of Indolent Systemic Mastocytosis

Treatment of ISM is intended to prevent mast cell mediator release and is mainly symptomatic.[9,60] ISM progresses slowly or not at all and most patients have normal life expectancy. Therefore, therapies to reduce mast cell numbers, which are associated with significant adverse effects, are generally not indicated or recommended. Treatment usually includes mediator-targeting drugs, including antihistamines, but does not usually require cytoreductive agents, except for considering IFN-2b for severe osteoporosis.[9,60]

SYSTEMIC MASTOCYTOSIS WITH ASSOCIATED CLONAL HEMATOLOGIC NON–MAST CELL LINEAGE DISEASE

Treatment of patients with SM-AHNMD depends on the associated hematologic condition. Generally, the approach is to treat AHNMD as if SM were not present and to treat the mastocytosis as if the AHNMD were not present. Successful treatment of the hematologic disorder has not been shown to change or improve their SM. The prognosis of patients with SM-AHNMD is that of the hematologic disorder present.

Treatment of Agressive Systemic Mastocytosis

ASM is a clonal mast cell disease characterized by progressive growth of neoplastic cells in diverse organs but most frequently affected are the bone marrow, skeletal system, liver, spleen, and the GI tract. Respective clinical findings (so called C-findings) include cytopenias, osteolysis (or osteoporosis) with pathologic fractures, hepatosplenomegaly with impaired liver function and ascites, and malabsorption. During the past decade, several treatment strategies for ASM have been proposed. One promising approach may be combination treatment with IFN alpha and glucocorticoids.[61,62]

The most commonly administered therapies are IFN alpha-2b, cladribine, glucocorticoids, tyrosine kinase inhibitors, and hydroxyurea. Cladribine is often reserved for patients who do not respond to IFN alpha. Prophylaxis to prevent *Pneumocystis jiroveci* pneumonia is suggested for at least 3 months after therapy is complete and until the CD4 count is greater than 200/μL. Orally administered glucocorticoids are helpful for patients with ASM and severe malabsorption or ascites and can be given as a 2-week to 3-week taper, although some patients may require low-dose maintenance therapy.

In patients with ASM, IFN alfa (with or without corticosteroids) can control dermatologic, hematological, GI, skeletal, and mediator-release symptoms but may be poorly tolerated. Cladribine has broad therapeutic activity, particularly when rapid debulking is indicated; the main toxicity is myelosuppression. Imatinib has a therapeutic role in the presence of an imatinib-sensitive KIT mutation or in patients with unmutated *KITD816*.[28] Imatinib is approved by the FDA for ASM in patients who do not have a D816V KIT mutation or those with unknown mutational status. Splenectomy may be indicated for hypersplenism in association with severe anemia and thrombocytopenia.[63]

Hydroxyurea has also been administered to patients with ASM and SM-AHNMD, mainly for the treatment of associated myeloproliferative disorders, although there are few published data on efficacy.

Hydroxyurea has few side effects compared with other chemotherapeutic agents, although hematologic toxicity and GI side effects may be problematic at higher doses. Patients should use contraception because hydroxyurea is a teratogen.

Mast Cell Leukemia

There is no approved standard therapy for MCL. There are few options are available for treatment and, because of the rarity of the disease, few clinical trials address the question.[29] Patients with MCL are often treated with polychemotherapy, similarly to those with acute leukemia. Administered agents have included cladribine, tyrosine kinase inhibitors, and polychemotherapy. Bone marrow transplantation may be considered, although sustained remission has not been reported.[29] Patients with MCL are particularly prone to GI bleeding due to heparin release from the high number of mast cells present and possibly associated coagulopathies,[64] and chronic proton pump inhibitor therapy should be considered for GI prophylaxis. Therapy usually fails and the median survival time is less than 6 months.

Mast Cell Sarcoma

MCS is an extremely rare and aggressive subtype of mastocytosis with poor prognosis. MCS is an aggressive tumor that exhibits an always fatal evolution despite various classic polychemotherapies with or without radiotherapy. The median survival is only 12 months, and no good treatment is available.[29]

Extracutaneous Mastocytoma

Treatment is surgical for extracuteneous mastocytomas, although they are extremely uncommon and prognosis is unknown due to its rarity.[65]

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