WE-S16-MPN-030

Primer on Advanced Mastocytosis

Robyn M. Scherber, MD[1,2,*]
[1]*Mays Cancer Center MD Anderson, San Antonio, TX 78229, USA*
[2]*Mayo Clinic, Scottsdale, AZ 85259, USA*
[*]**Corresponding author:** Scherber@uthscsa.edu

Keywords
mast cell leukemia, midostaurin, imatinib, masitinib, BLU-285

Introduction

Following the first documented case of utricaria pigmentosa in 1869,[1] our understanding of mast cell diseases has greatly expanded. Systemic Mastocytosis (SM) is characterized by aberrant clonal mast cell activation and accompanied by heterogeneous symptoms that are often caused by vasoactive mediators. Somatic activating mutations in the KIT gene, most often the KIT Asp816Val D816V mutation in the CD117 receptor, help to define the disease and represent key mutations in the pathogenesis of SM that are present in most patients. This format is to be used for submissions that are published in the annual meeting proceedings publication. The easiest way to adhere to the format in this sample document is to replace this content with your own material.

Presentation

Most patients with SM will present with an unusual symptom profile that can include failure to thrive, rashes, atypical allergies, and anaphylaxis. The unique constellation of symptoms based on literature review is demonstrated in Figure 1. Triggers to symptoms can include heat, allergens, contrast dyes, stress, and medications (i.e., NSAIDS, opioids), and severe reactions may require the use of epinephrine. For patients who present with these features, the differential diagnosis should also include alternative autoimmune (i.e., celiac disease), endocrine (i.e., pheochromocytoma), malignant (i.e., carcinoid), or neurologic conditions (i.e., depression). If no clonal source of mast cell activation is found, the diagnosis of non-clonal mast cell activation syndrome (MCAS) should also be considered. This diagnosis is made in the presence of: 1) typical mast cell release symptoms, 2) a serum total tryptase by >20% above baseline plus 2 ng/mL within 4 hours of symptoms, and 3) response to mast cell blocking agents.[2]

Figure 1 Features of systemic mastocytosis in the bone marrow demonstrating scattered mast cells (arrows) with variable granulation, often grouped in a multifocal cluster infiltration pattern. Image courtesy of ASH Image Bank. Obtained at: http://imagebank.hematology.org/image/4052/systemic-mastocytosis–1?type=upload.

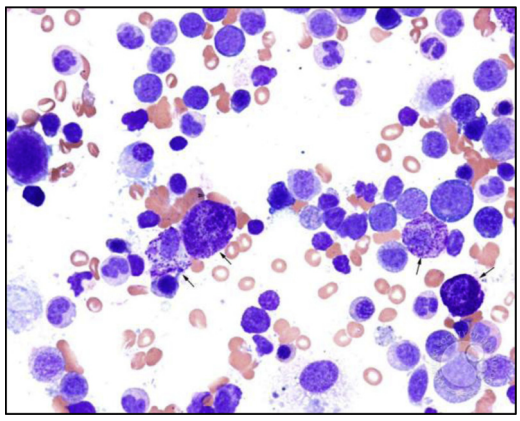

Table 1 SM Clinical-molecular Prognostic Model

Variable	Score allotment
Platelet count <150 3 10^9/L	2 points
Serum albumin <3.5 g/dL	1.5 points
Hemoglobin <10 g/dL or RBC transfusion dependence	1 point
Age >60 years	1.5 points
ASXL1 mutation	1.5 points
Risk Score (cumulative points)	**Median Survival**
Low risk (0-1.5)	86 months
Intermediate Risk (2-4.5)	21 months
High Risk (5-7.5)	5 months

Diagnosis

Serum tryptase is elevated in the majority of SM patients and determination aids greatly in the identification and diagnosis of this clonal disorder. The degree of elevation of serum tryptase has also been found to be correlated ($r = 0.8$)[3] with the grade of bone marrow mast cell infiltration. Mast cell infiltration can also be found in the skin, colon, or liver, so organ

dysfunction or symptoms within these organ systems should be investigated with the preference for biopsy with staining for CD2 and/or CD25 if applicable. Again of function C-KIT mutation is present in greater than 90% of patients, with the specific KIT D816V mutation[4,5] being most frequent. In patients where there is a low suspicion for SM, peripheral blood CKIT testing and serum tryptase can help to delineate whether a clonal mast cell cause of

Table 2 Therapies for symptom control

Symptom	Drug class
Pruritus, flushing	H1-antagonist
	Leukotriene antagonist
	Nonsteroidal anti-inflammatory drug
	Psolaren plus UV A photochemotherapy
	Omalizumab
Abdominal pain, cramping, diarrhea, heartburn, nausea, vomiting	H2-antagonist
	Proton pump inhibitor
	Cromolyn
	Corticosteroid
Headache, cognitive impairment, depression	H1- and H2-antagonist
	Sodium cromolyn
Recurrent hypotension	Epinephrine
	H1- and H2-antagonists
	Corticosteroid
	Cytoreductive therapy (IFN-α or 2-chlorodeoxyadenosine)
Osteoporosis	Bisphosphonate
	Cytokine/ immunomodulatory drug
	Purine nucleoside analog

symptoms is present. For patients where there is intermediate or high suspicion of SM, evaluation should include a thorough history of symptoms and triggers, physical examination including lymph nodes and spleen assessment, and laboratory assessment for C-KIT mutational testing and serum tryptase. The formal diagnosis of SM should be per the World Health Organization (WHO) diagnostic criteria of SM[6], and include the assessment of B-findings (i.e., >30% bone marrow infiltrates or serum tryptase >200ng/mL, dysplasia or myeloproliferation in non-mast cell lineages, hepatomegaly or splenomegaly without organ dysfunction) and C- findings (i.e., cytopenias without other known source, hepatomegaly or splenomegaly with organ dysfunction, skeletal involvement and GI involvement with malabsorption).

A key comparison of indolent and smoldering SM is the presence of at least two B-findings being characteristic of the latter. The categorization of the SM subtype is inherently prognostic, with the presence of C findings being a key characterization of aggressive SM. However, outside of the WHO criteria, alternative prognostic models have also been developed which take into account laboratory findings, age and mutational status (Table 1) based on registry findings.[7]

Treatment

Initial treatment, particularly in cases of more indolent types of SM or in highly symptomatic patients generally includes symptom control as demonstrated in Table 2.[8,9] Continued monitoring and adjustment of symptom oriented therapy, as well as development or progression of B- or C-findings, is key in cutaneous, indolent, and smoldering SM. Efforts should also be taken to avoid triggers of mast cell activation. Patients should also be prescribed an emergency epinephrine injector. Cutaneous SM can typically be treated with localized treatment (i.e., PUVA, topical steroids), although oral psoralen or steroids can also be considered in combination.[10] Additionally, bone density should be considered for treatment in patients whose life expectancy and physical functioning warrant treatment.[11,12]

Treatment for progressive SM (i.e., rapid onset end-organ dysfunction due to mast cell infiltrates or rapid consistent rise in tryptase levels), aggressive SM, and MCL has recently changed in light of midostaurin U.S. Food and Drug Administration approval in 2017 (Table 3). Prior to this, imatinib was the only approved agent for use of aggressive SM without the D816V C-KIT mutation. Midostaurin is well tolerated, with most frequent adverse events being nausea, vomiting, and diarrhea.

Investigational Agents

Despite the activity of midostaurin, alternative C-KIT inhibitors, namely, the highly selective KIT D816V inhibitor BLU-285, are being investigated for use in the more aggressive SM subtypes. BLU-285 has significant activity against the KIT D816V mutation with in vitro and in vivo testing, even in cases which are resistant to midostaurin.[13] BLU-285 appears to be very well tolerated with most adverse events being grade 1 and no grade 4 events. Grade 2 events included fatigue, dizziness, headache, rash, shingles, anemia, elevated GGT and thrombocytopenia. A new agent that recently underwent phase III testing is masitinib, an inhibitor of KIT, FLN, and LYN kinases.[14] Side effects were non life- threatening and included diarrhea, rash, and asthenia. No life-threatening toxicities occurred. In cases of eosinophilia with accompanying rearrangement of PDGFRA or harbor mutations C-kit mutations outside of exon 17, novel tyrosine kinase inhibitors are being investigated.[15,16] Dasatinib has some demonstrated activity to block the tyrosine kinase activity of C-KIT D816V and has shown activity in

Table 3 Select studies of therapeutic targets and treatments in aggressive SM

Drug	Mutation or disease subtype
Midostaurin	Advanced SM[28]
Imatinib	C-Kit Exon 9[16]
	C-Kit Exon 9, *A1547T*[29]
Masitinib	Smoldering SM[14]
Dasatinib	Indolent SM, Aggressive SM, and SM-AHNMD[30]
Interferon	Individuals meeting WHO SM diagnostic criteria[31]
Hydroxyurea	SM with BM involvement[19]
	Individuals meeting WHO SM diagnostic criteria[31]
2-chlorodeoxyadenosine (2-CdA)	Individuals meeting WHO SM diagnostic criteria[31]
	Indolent and advanced SM[20]