Clinical Presentation and Diagnosis of Advanced Systemic Mastocytosis in a Community Oncology Setting

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Context & Objective

- Systemic mastocytosis (SM) is a rare hematologic disease characterized by the accumulation of abnormal mast cells in tissues or organs. SM affects multiple organ systems including the skin, gastrointestinal tract, and cardiovascular system.[1,2,3]
- SM is characterized as either advanced (AdvSM) or non-advanced (non-AdvSM). AdvSM can be differentiated further into subtypes including SM with associated hematologic neoplasm (SM-AHN), mast cell leukemia (MCL), and aggressive SM (ASM).[4,5]
- AdvSM is less prevalent than non-AdvSM and has an estimated prevalence of up to 3.9 patients per million.[6]
- Patients with AdvSM have a poor prognosis and decreased life expectancy.[7]
- The *KIT* D816V mutation is present in 95% of patients with AdvSM; however, the condition often poses a diagnostic challenge due to the substantial variation in the disease's clinical presentation, resulting in a median time of 3 years between symptom onset and diagnosis.[1,2,3,8]
- The objectives of this study were to characterize the physicians treating AdvSM patients, to characterize the presentation of AdvSM patients, and to understand referral, diagnosis, and treatment patterns of AdvSM patients in community-based oncology practices.

Design & Setting

- Community oncologists affiliated with IntegraConnect were invited to complete a structured electronic case report form (eCRF) developed by IntegraConnect physician thought leaders.
- The eCRF was available for completion between August and November 2021.
- Eligible physicians reported treating at least one AdvSM patient in the prior 24 months and could complete the eCRF more than once if they treated more than one patient.
- The eCRF included questions on referral patterns, patient signs and symptoms at initial visit, approach to diagnosis, and ongoing disease management.

Results

Physician Demographics and Practice Setting

- Twenty-eight community oncologists completed the eCRF and represented various types of organizations including office-based practices (78%), university or medical schools (11%), teaching hospitals (7%), and cancer centers (4%) (**Table 1**).
- Most physicians worked in private practice (68%), followed by academic teaching hospitals (14%), community-based hospitals (11%), and specialized treatment facilities (8%) (**Table 1**).
- In the 3 years prior to the study, the physicians' clinics treated a total of 98 patients with cutaneous mastocytosis (CM). Two-hundred and thirteen SM patients were treated in that time: 81 patients with aggressive systemic mastocytosis (ASM), 54 patients with indolent systemic mastocytosis (ISM), 40 patients with smoldering systemic mastocytosis (SSM) and 38 patients with systemic mastocytosis with associated hematological neoplasm (SM-AHN). Twenty-five patients with mast cell leukemia (MCL) were also treated (**Table 1**).
- Most physicians (75%) treated 3 or more SM patients, and 21% of physicians treated more than 5 SM patients in the 3 years leading up to the study (**Table 1**).

Patient Characteristics

- The sample included 55 patients with AdvSM who were primarily female (55%), between 50 and 70 years of age, with an average of 2.3 comorbidities per patient (**Table 2, Figure 1**).
- The most common comorbidities included cardiovascular disease (38%), diabetes mellitus (38%), gastroesophageal reflux disease (GERD) (29%), asthma/chronic obstructive pulmonary disorder (COPD) (25%), and obesity (22%) (**Table 2**).
- Seventy-nine percent of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (**Table 2**).

Referral and Diagnosis

- Patients were referred to the community oncology clinics by various practitioners, including primary care physicians, immunologists, dermatologists, other oncologists, rheumatologists, and other specialists (**Figure 2**).
- Bone marrow biopsy was performed in virtually all patients (**Table 3, Figure 3**) and was reported to be a critical factor in establishing a diagnosis of AdvSM in 93% of cases.
- Physicians reported using serum tryptase and *KIT* mutation detection tests to confirm diagnosis 87% and 75% of the time, respectively (**Figure 3**).
- The most common signs and symptoms that were reported during initial visit included pruritis, fatigue/tiredness, flushing, nausea, and bloating, maculopapular cutaneous mastocytosis (MCPM), splenomegaly, nodules, urticaria pigmentosa, and lymphadenopathy (**Table 5**).
- The most common sign/symptom categories that were observed in SM patients during initial visit were cutaneous and gastrointestinal in nature (**Figure 5**).

Treatment

- Physicians reported their primary reason for selection of first-line treatments was decreasing the symptom burden, familiarity with treatment and improving patient quality of life. Similarly, treatment familiarity and reducing of mast cell/symptom burden, along with providing a durable response were primary reasons for selection of second line treatment (**Figure 4**).
- Responding physicians reported large unmet needs, with 96% believing there is unmet need in the treatment options for patients with AdvSM.

Conclusions

- This study found that patients with AdvSM are referred to community-based oncologists by practitioners across many diverse specialty types, including primary care, oncology, dermatology, and endocrinology.
- Patients with AdvSM frequently have comorbid conditions and present to community oncologists for their initial visit with heterogenous signs and symptoms affecting multiple organ systems.
- Inadequate response is the biggest reason for treatment discontinuation, showing that current treatment options are suboptimal.
- Increased awareness of AdvSM diagnosis and management among clinicians may help to increase disease recognition, shorten the time to diagnosis, and expedite treatment initiation.

References

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Disclosures

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Results (continued)

Figure 1. Patient Age Distribution

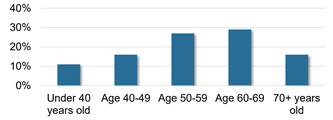


Table 1. Physician and Practice Characteristics

	Physicians (n=55)	
Primary Practice Setting	**n**	**%**
Non-Affiliated Private Practice	12	43%
Affiliated Private Practice	7	25%
Academic Teaching Hospital	4	14%
Community-Based Hospital	3	11%
Affiliated Specialized Clinic or Treatment Center	1	4%
Non-Affiliated Specialized Clinic or Treatment Center	1	4%
Organization Type		
Office-Based Practice, Group Purchasing Org. (GPO)	14	50%
Office-Based Practice, Hospital	4	14%
University/Medical Based, Hospital	3	11%
Office-Based Multidisciplinary private practice w/o GPO	2	7%
Office-Based Specialty Practice w/GPO	2	7%
Hospital Based Teaching Hospital	2	7%
Cancer Center	1	4%
Number of Physicians in Practice		
1 to 5	3	11%
6 to 10	8	29%
11 to 15	6	21%
16 to 20	3	11%
> 20	8	29%
Number of SM patients treated in past 3 years		
One	7	25%
Two	3	11%
Three	7	25%
Four	5	18%
≥ 5	6	21%
Number of Patients Treated in Past 3 Years		
Cutaneous mastocytosis	98	N/A
Aggressive systemic mastocytosis	81	N/A
Mast Cell Activation Syndrome	74	N/A
Indolent systemic mastocytosis	54	N/A
Smoldering systemic mastocytosis	40	N/A
SM-AHN	38	N/A
Mast cell leukemia	25	N/A

Figure 2. Referring Physician Specialty

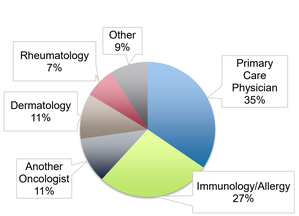


Table 2. Patients Demographics and Comorbidities

	Patients (n=55)	
EGOG Performance Status	**n**	**%**
0	13	24%
1	30	55%
2	12	22%
Common Comorbidities		
Cardiovascular condition	21	38%
Diabetes mellitus	21	38%
GERD	16	29%
COPD/Asthma	14	25%
Obesity	12	22%
Arthritis	11	20%
Osteoporosis or osteopenia	10	18%
Chronic kidney disease	9	16%
Sleep disorder	8	15%
Thromboembolic disease	7	13%
None	7	13%
Cancer	3	5%
Current infection	2	4%
Other	2	4%

Abbreviations: SM-AHN, Systemic mastocytosis with associated hematologic neoplasm; ECOG, Eastern Cooperative Oncology Group; COPD, chronic obstructive pulmonary disease; GERD, Gastro-esophageal reflux disease; OS, overall survival; QOL, quality of life

Table 3. Referral and Diagnostic Patterns

	AdvSM Patients (n=55)	
	n	**%**
Physicians Seen Prior to Oncology		
Primary Care Physician	35	64%
Immunology/Allergy	24	44%
Dermatology	22	40%
Pulmonology	12	22%
Gastroenterology	11	20%
Rheumatology	10	18%
Another Oncologist	8	15%
Infectious disease	3	5%
Surgical Speciality	2	4%
Imaging at Diagnosis		
CT	52	95%
PET	6	11%
MRI	2	4%
Ultrasound	1	2%
Critical Steps in Diagnosis		
Bone marrow biopsy	51	93%
Elevated serum tryptase	35	64%
Detection of *KIT* D816V mutation	31	56%
Expert pathologist	25	45%
Other biopsy	4	7%
Symptoms of anaphylaxis	1	2%
Accurate Diagnosis		
Initially Diagnosed with AdvSM	46	84%
Initially Diagnosed with other form of SM	5	9%
Initially misdiagnosed	4	7%

Table 4. Reasons for Treatment Discontinuation[a,b,c]

	1L Treatment (n=30)		2L Treatment (n=15)	
	n	**%**	**n**	**%**
Suboptimal response	19	63%	8	53%
Tolerability concerns	5	17%	5	33%
Compliance issues	5	17%	6	40%
GI toxicity	4	13%	7	46%
Adverse effects	2	7%	0	0%
Patient death	2	7%	0	0%
Disease progression	1	3%	0	0%

Figure 5. % Patients Experiencing Symptom Domain (n=55)

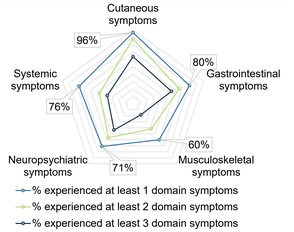
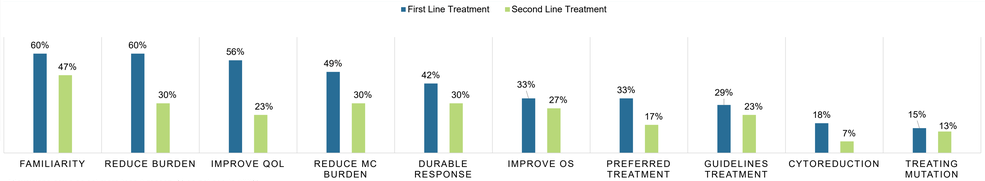


Table 5. Patient Signs and Symptoms at Initial Visit

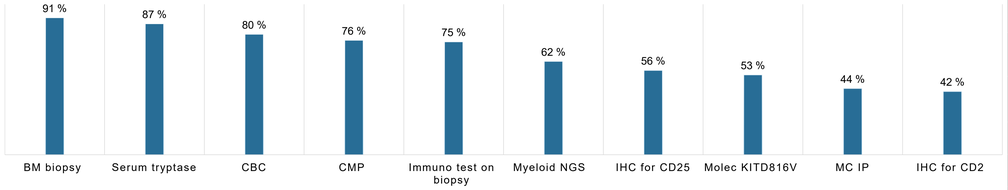
	AdvSM Patients (n=55)	
	n	**%**
Pruritus	37	67%
Maculopapular cutaneous mastocytosis (MCPM)	35	64%
Fatigue/tiredness	35	64%
Flushing	34	62%
Nausea	32	58%
Bloating	30	55%
Diarrhea	29	53%
Abdominal cramping	27	49%
Anxiety	27	49%
Headaches	27	49%
Splenomegaly	26	47%
Nodules	24	44%
Diffuse pain in the long bones	24	44%
Urticaria pigmentosa	23	42%
Abdominal pain	23	42%
Irritability	23	42%
Allergic reactions	22	40%
Poorly localized bone pain	21	38%
Dyspnea	19	35%
Insomnia	18	33%
Peptic ulcer disease	17	31%
Hepatomegaly	17	31%
Lymphadenopathy	17	31%

Figure 4. Physician-Reported Reasons for First and Second-Line Treatment Selection[a,b,c]



[a]Physicians could select more than 1 reason, % do not add to 100%
[b]1 Not all patients started on 2L treatment, so percent of physicians reported reasons for 2L initiation and discontinuation is lower than 1L
[c]Medications providers reported discontinuing: midostaurin, imatinib, montelukast, dasatinib, brentuximab vedotin, zilleuton, zafirlukast, zilleuton, antihistamines, cromolyn sodium, interferon-alpha, cladribine, azacitidine, and hydroxyurea

Figure 3. Proportion of Physicians Reporting Diagnostic Test Use



Abbreviations in order of preference: Bone marrow biopsy, Serum total tryptase level, CBC with differential, Complete Metabolic Panel (CMP), Immunohistochemistry for *KIT* CD117 performed on biopsy, Next Generation Sequencing (NGS) panel for myeloid malignancies, IHC for CD25 performed on biopsy, Molecular testing for *KIT* D816V mutation specifically, Mast Cell Immunophenotyping by Flow cytometry, IHC for CD2 performed on biopsy. Physicians could report using more than 1 test

Table 6. Patient Signs/Symptoms in Domains at Initial Visit to Community Oncology

Symptom Domain	% Pts Reporting 1+ Symptom	% Pts Reporting 2+ Symptoms	% Pts Reporting 3+ Symptoms	Signs/Symptoms In Domain
Cutaneous Signs/Symptoms	96.4%	87.3%	63.6%	Flushing, Pruritus, Maculopapular Cutaneous Mastocytosis (MCPM), Nodules, Other Skin Changes, Plaque-like Lesions, Urticaria Pigmentosa
Gastrointestinal Sign/Symptoms	80.0%	65.5%	54.5%	Abdominal Cramping, Abdominal Pain, Bloating, Diarrhea, Gastrointestinal Bleeding, Malabsorption, Nausea, Steatorrhea, Vomiting, Peptic Ulcer Disease
Musculoskeletal Signs/Symptoms	60.0%	41.8%	18.2%	Osteopenia, Osteoporosis, Osteoporotic Fractures, Diffuse Pain In The Long Bones, Poorly Localized Bone Pain
Neuropsychiatric Signs/Symptoms	70.9%	56.4%	43.6%	Anxiety, Emotional Instability, Headaches, Increased Somnolence, Insomnia, Irritability, Cognitive Deficits, Short-term Memory Loss
Systemic Signs/Symptoms	76.4%	47.3%	36.4%	Anaphylaxis, Angioedema, Hepatomegaly, Allergic Reactions, Dyspnea, Fatigue/Tiredness

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