National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Systemic Mastocytosis

NCCN Evidence Blocks™

Version 2.2019 — December 3, 2018

NCCN.org

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Systemic Mastocytosis
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

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NCCN Guidelines Panel Disclosures

Continue

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Systemic Mastocytosis
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
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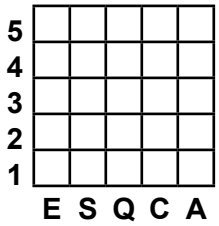
Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/clinicians.aspx.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

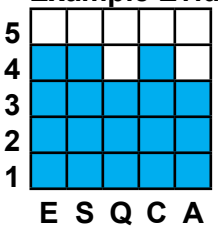
See NCCN Categories of Evidence and Consensus.

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

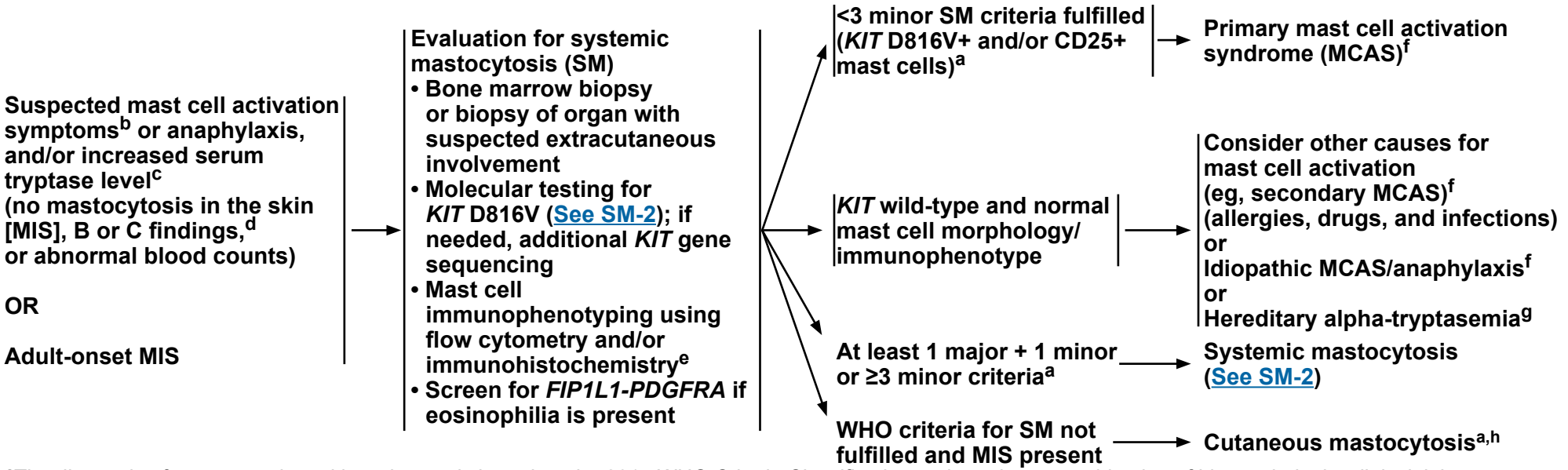
Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

DIAGNOSTIC ALGORITHM FOR THE PATIENT PRESENTING WITH SIGNS OR SYMPTOMS OF MASTOCYTOSIS[a]



[a]The diagnosis of mastocytosis and its subtypes is based on the 2017 WHO Criteria Classification and requires a combination of histopathologic, clinical, laboratory, and cytogenetic/molecular analyses. See 2017 World Health Organization Classification of Mastocytosis (SM-A); see 2017 WHO Diagnostic Criteria for Cutaneous and Systemic Mastocytosis (SM-B); and see 2017 Diagnostic Criteria for the Variants of Systemic Mastocytosis (SM-C).

[b]Patients should be counseled about the signs/symptoms and potential triggers of mast cell activation (See SM-H). Multidisciplinary collaboration with sub-specialists (eg, anesthesia for procedures/surgery; high-risk OB for pregnancy) is recommended.

[c]Serum tryptase level may be <20 ng/mL or only transiently elevated.

[d]See WHO Criteria for B-Findings and C-Findings in Patients with Systemic Mastocytosis (SM-D) and IWG-MRT-ECNM Criteria for Eligible Organ Damage to Assess Clinical Improvement (CI) and Treatment Response (SM-E). B- and C-findings are used for the diagnosis of the WHO subtype of SM (SM-C and SM-D) and IWG-MRT-ECNM criteria are used to establish eligible organ damage findings for clinical trial enrollment and to adjudicate response to therapy (SM-E).

[e]Mast cell markers by flow cytometry immunophenotyping include CD117, CD25, and CD2. Immunohistochemistry markers include CD117, CD25, and tryptase. For both techniques, CD30 is optional. Also see SM-2.

[f]Specific criteria have been established for primary and secondary MCAS (Akin C. Mast cell activation syndromes. J Allergy Clin Immunol 2017;140:349-355). Primary MCAS has also been referred to as monoclonal mast cell activation syndrome (MMAS). (See Discussion).

[g]Hereditary alpha-tryptasemia is a multi-system disorder characterized by duplications and triplications in the TPSAB1 gene encoding α-tryptase associated with elevation of the basal serum tryptase level and symptoms including cutaneous flushing and pruritus, dysautonomia, functional gastrointestinal symptoms, chronic pain, and connective tissue abnormalities, including joint hypermobility. Lyons JJ, Yu X, Hughes JD, et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. Nat Genet 2016;48:1564-1569.

[h]Management of cutaneous mastocytosis is not included in these guidelines. Referral to centers with expertise in cutaneous mastocytosis is strongly recommended.

Adapted from: Pardanani A. Systemic mastocytosis in adults: 2017 update on diagnosis, risk stratification and management. Am J Hematol 2016;91:1146-1159.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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WORKUP FOR SUSPECTED SYSTEMIC MASTOCYTOSIS[i]

General Diagnostic Studies

- H&P, including, prior history of mast cell activation symptoms; potential triggers; examination for MIS; spleen and liver size by palpation; documentation of medications, transfusion history, and weight loss
- Comprehensive metabolic panel with uric acid, lactate dehydrogenase (LDH), and liver function tests (LFTs)
- Serum tryptase level
- CBC with differential
- Examination of blood smear (eg, monocytosis, eosinophilia, dysplasia)[j]
- Bone marrow aspirate and biopsy with[j]:
  - Flow cytometry: CD34, CD117, CD25, CD2; CD30 (optional)
  - Immunohistochemistry: CD117, CD25, tryptase; CD30 (optional)
- Cytogenetics
- FISH as needed for associated hematologic neoplasm (AHN)-related abnormalities[j]
- Molecular testing for *KIT* D816V by allele-specific PCR or alternative high-sensitivity method[j,k,l]
- Myeloid mutation panel (eg, containing *SRSF2, ASXL1, RUNX1*)[j,l]

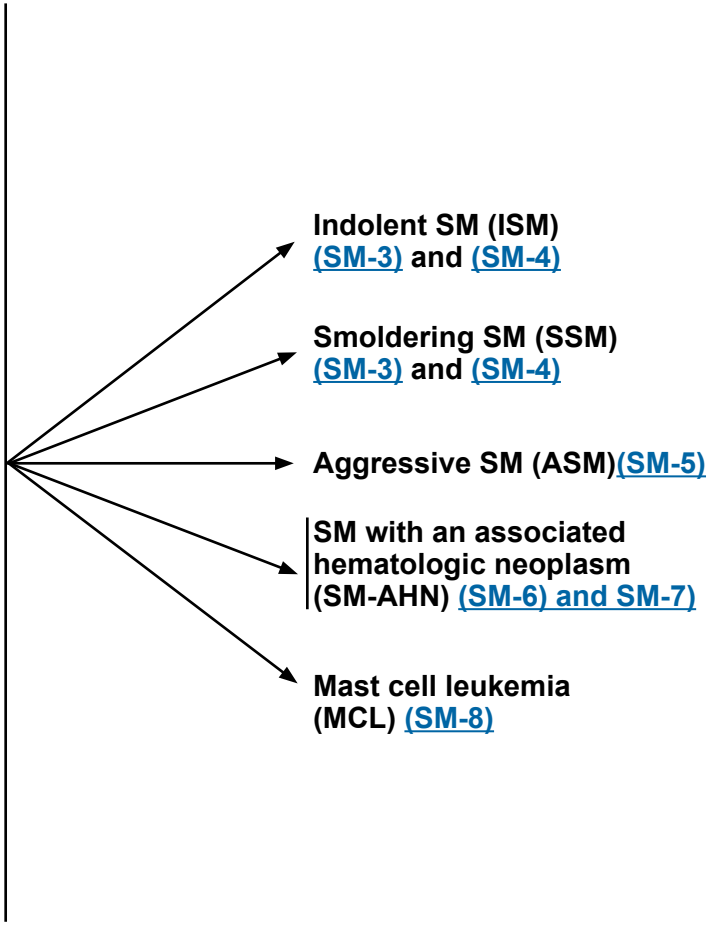
Evaluation of B- and C-Findings and Organ Involvement[d]

- CT/MRI or ultrasound of the abdomen/pelvis
- DEXA scan to evaluate for osteopenia/osteoporosis
- Metastatic skeletal survey to evaluate for osteolytic lesions
- Organ-directed biopsy (eg, endoscopy, liver biopsy) as needed with immunohistochemistry (CD117, CD25, tryptase, and CD3 as a control T-cell marker)

Useful Under Selected Circumstances

- 24-hour urine studies for biochemical evidence of mast cell activation
  - N-methylhistamine
  - Prostaglandin D2
  - 2,3-Dinor-11beta-prostaglandin F2 alpha
- HLA testing, if considering allogeneic hematopoietic cell transplant (HCT)
- Assessment of symptom burden and quality of life (QOL) using the Mastocytosis Symptom Assessment form (MSAF) and the Mastocytosis Quality of Life Questionnaire (MQLQ)[m]

CLASSIFICATION[i]



[d] See WHO Criteria for B-Findings and C-Findings in Patients with Systemic Mastocytosis (SM-D) and IWG-MRT-ECNM Criteria for Eligible Organ Damage to Assess Clinical Improvement (CI) and Treatment Response (SM-E). B- and C-findings are used for the diagnosis of the WHO subtype of SM (SM-C and SM-D) and IWG-MRT-ECNM criteria are used to establish eligible organ damage findings for clinical trial enrollment and to adjudicate response to therapy (SM-E).

[i] See 2017 Diagnostic Criteria for the Variants of Systemic Mastocytosis (SM-C).

[j] See Recommendations for Histopathology Analysis (SM-G 1 of 3).

[k] Preferred on the bone marrow, as yield from the peripheral blood may be lower; exceptions may be patients with SM-AHN or MCL. See Recommendations for *KIT* D816V Mutation Testing in Systemic Mastocytosis (SM-G 2 of 3).

[l] See Adverse Prognostic Variables in Systemic Mastocytosis (SM-G 3 of 3).

[m] van Anrooij D, Kluin-Nelemans JC, Safy M, et al. Allergy 2016;71:1585-1593. MSAF and MQLQ have been validated only in patients with ISM, not in patients with more advanced forms of mast cell disease. To access the questionnaires for MSAF and MQLQ, select "Supporting Information" and "See Appendix S1 and Appendix S2."

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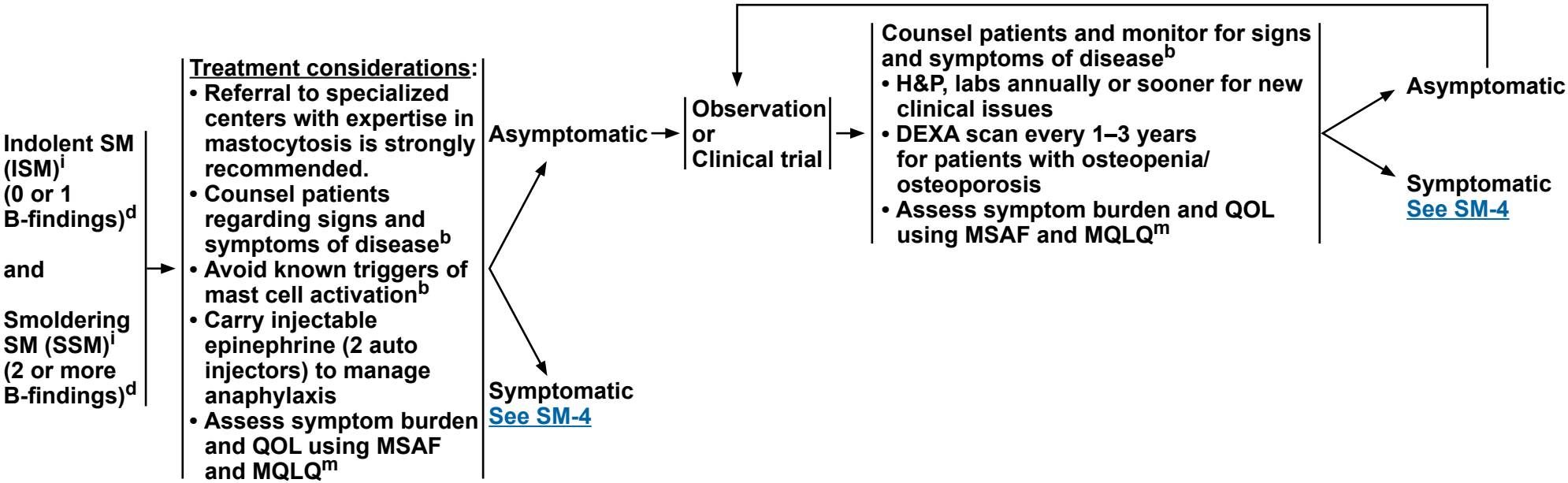
TREATMENT FOR INDOLENT SYSTEMIC MASTOCYTOSIS (ISM) AND SMOLDERING SYSTEMIC MASTOCYTOSIS (SSM)



Continued

[b]Patients should be counseled about the signs/symptoms and potential triggers of mast cell activation (See SM-H). Multidisciplinary collaboration with sub-specialists (eg, anesthesia for procedures/surgery; high-risk OB for pregnancy) is recommended.

[d]See WHO Criteria for B-Findings and C-Findings in Patients with Systemic Mastocytosis (SM-D) and IWG-MRT-ECNM Criteria for Eligible Organ Damage to Assess Clinical Improvement (CI) and Treatment Response (SM-E). B- and C-findings are used for the diagnosis of the WHO subtype of SM (SM-C and SM-D) and IWG-MRT-ECNM criteria are used to establish eligible organ damage findings for clinical trial enrollment and to adjudicate response to therapy (SM-E).

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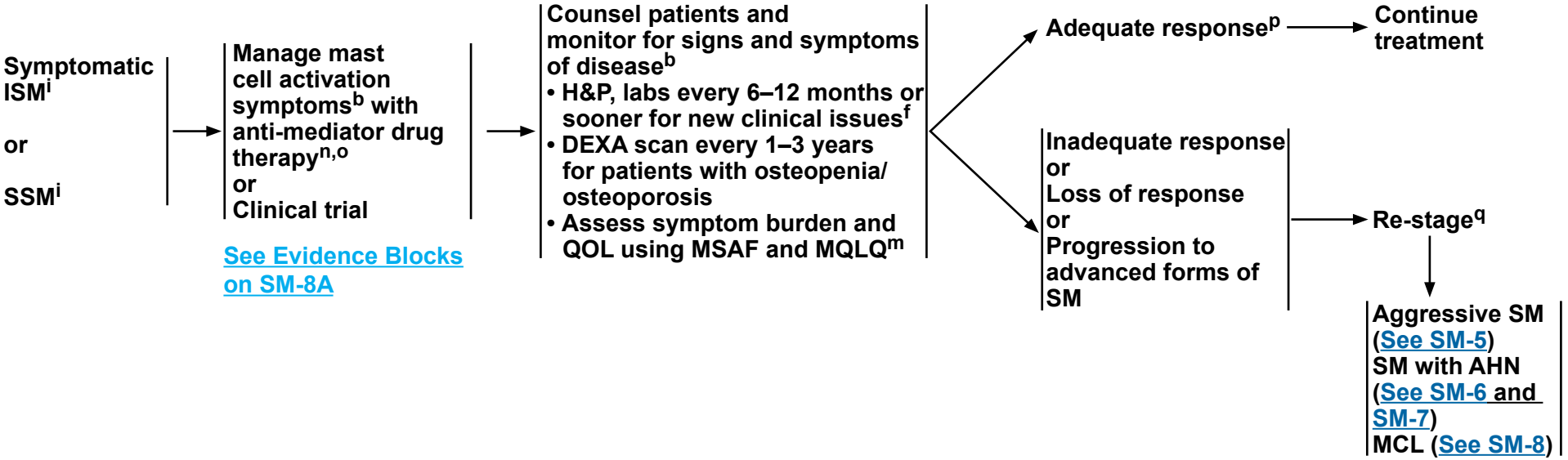

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[n]See (SM-I) for anti-mediator drug therapy approaches for mast cell activation symptoms.

[o]Cladribine and [PEG]-interferon-alfa are generally recommended only for patients with advanced SM. However, these agents may also be useful in selected patients with indolent or smoldering SM with severe, refractory mediator symptoms or bone disease not responsive to anti-mediator therapy or bisphosphonates.

[p]Response assessment should be based on improvement of disease-related symptoms and/or improvement of B-findings in ISM or SSM.

[q]Bone marrow aspirate and biopsy, serum tryptase level, and additional staging studies should be performed as clinically indicated (if supported by increased symptoms and signs of progression). See Discussion.

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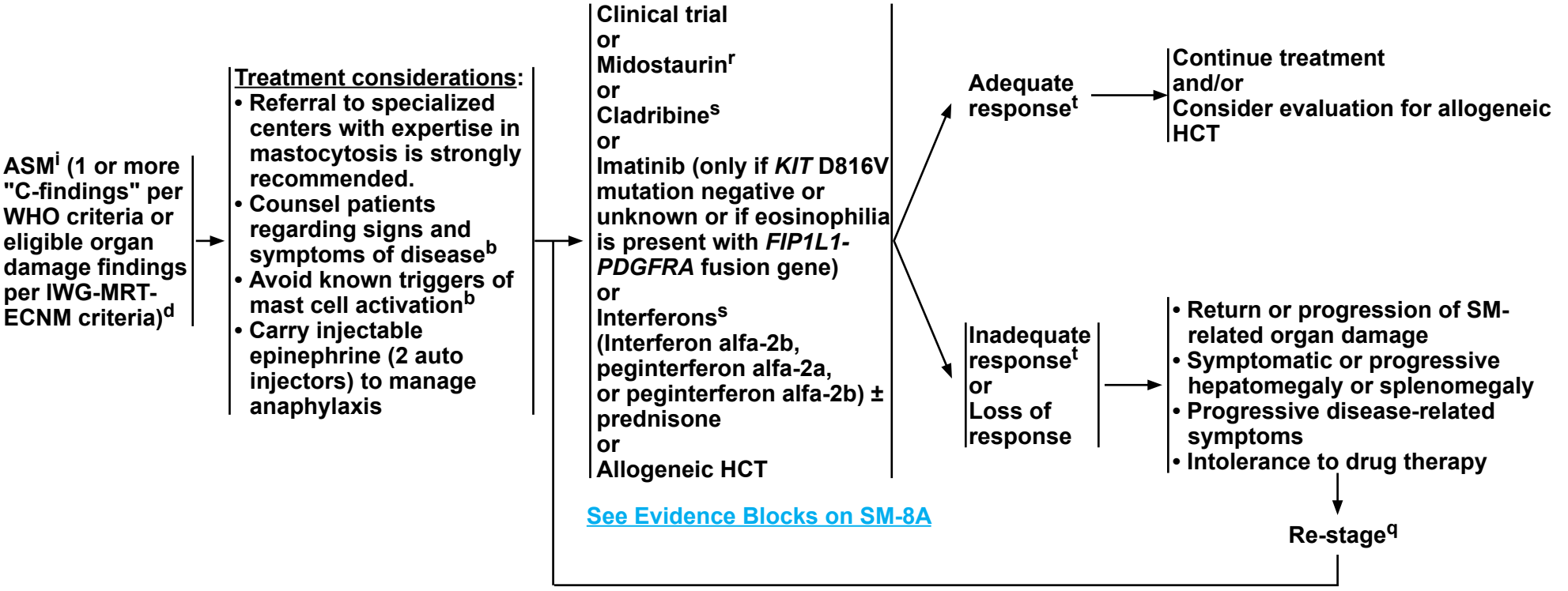
TREATMENT FOR AGGRESSIVE SYSTEMIC MASTOCYTOSIS (ASM)



[b]Patients should be counseled about the signs/symptoms and potential triggers of mast cell activation (See SM-H). Multidisciplinary collaboration with sub-specialists (eg, anesthesia for procedures/surgery; high-risk OB for pregnancy) is recommended.

[d]See WHO Criteria for B-Findings and C-Findings in Patients with Systemic Mastocytosis (SM-D) and IWG-MRT-ECNM Criteria for Eligible Organ Damage to Assess Clinical Improvement (CI) and Treatment Response (SM-E). B- and C-findings are used for the diagnosis of the WHO subtype of SM (SM-C and SM-D) and IWG-MRT-ECNM criteria are used to establish eligible organ damage findings for clinical trial enrollment and to adjudicate response to therapy (SM-E).

[i]See 2017 Diagnostic Criteria for the Variants of Systemic Mastocytosis (SM-C).

[q]Bone marrow aspirate and biopsy, serum tryptase level, and additional staging studies should be performed as clinically indicated (if supported by increased symptoms and signs of progression). See Discussion.

[r]For management of midostaurin toxicity, see SM-K.

[s]For patients with advanced SM, cladribine may be particularly useful when rapid debulking of disease is required whereas [PEG]-interferon alfa, which has a cytostatic mechanism of action, may be more suitable for patients with slowly progressive disease without the need for rapid cytoreduction.

[t]See 2013 IWG-MRT-ECNM Consensus Response Criteria (SM-F). Clinical benefit may not reach the threshold of the 2013 IWG-MRT-ECNM response criteria.

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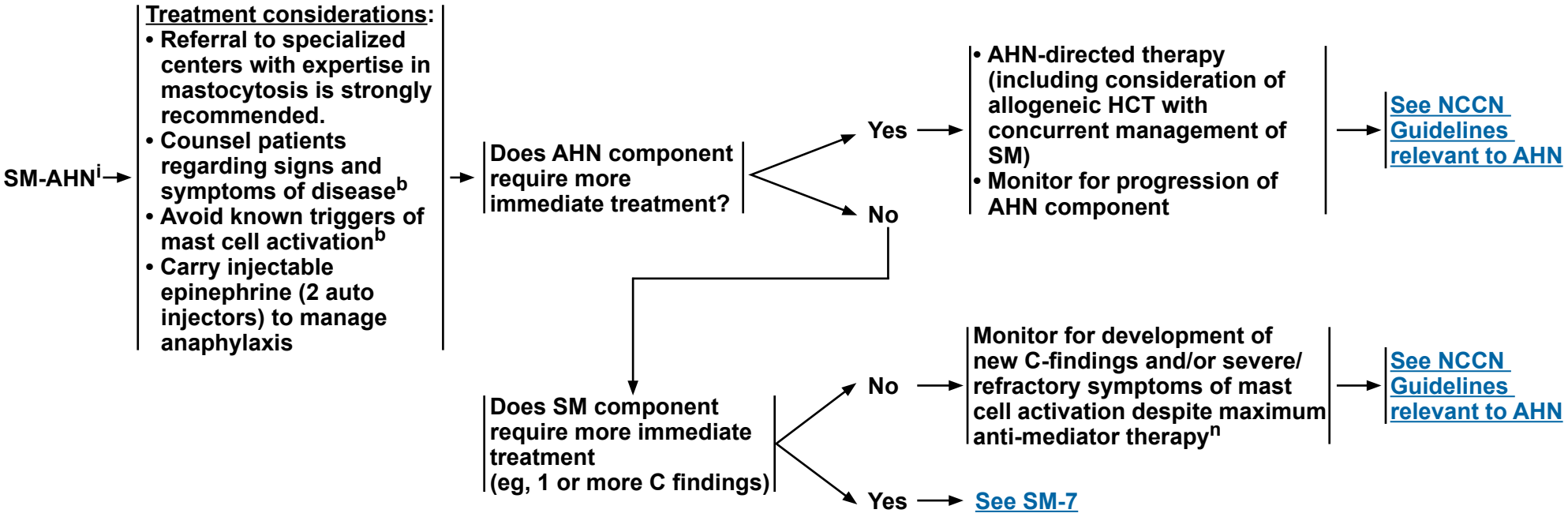
TREATMENT FOR SYSTEMIC MASTOCYTOSIS WITH AN ASSOCIATED HEMATOLOGIC NEOPLASM (SM-AHN)



[b]Patients should be counseled about the signs/symptoms and potential triggers of mast cell activation (See SM-H). Multidisciplinary collaboration with sub-specialists (eg, anesthesia for procedures/surgery; high-risk OB for pregnancy) is recommended.
[i]See 2017 Diagnostic Criteria for the Variants of Systemic Mastocytosis (SM-C).
[n]See (SM-I) for anti-mediator drug therapy approaches for mast cell activation symptoms.

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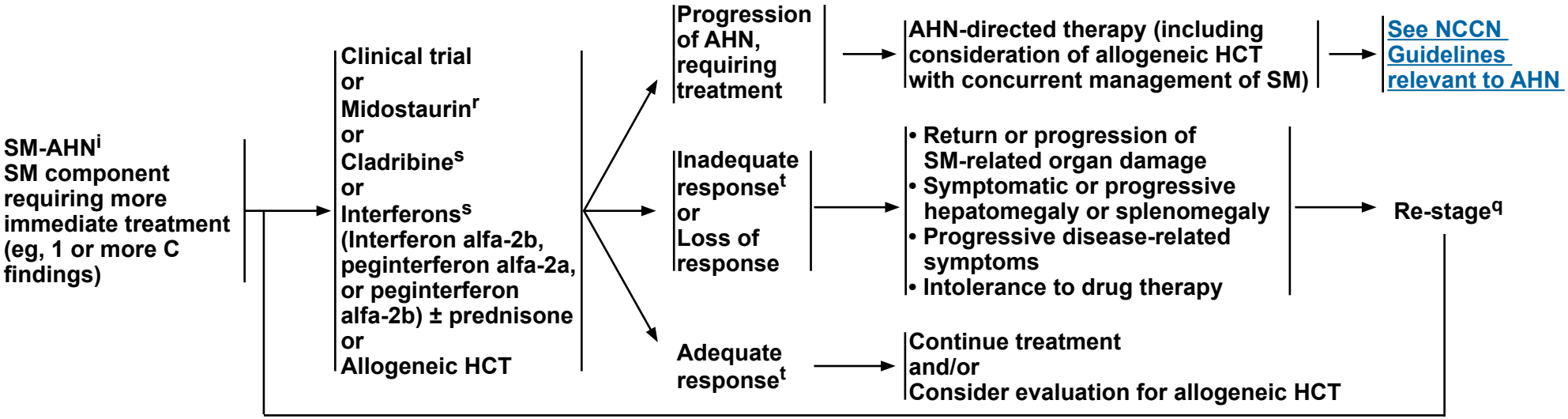

See Evidence Blocks on SM-8A

[i] See 2017 Diagnostic Criteria for the Variants of Systemic Mastocytosis (SM-C).

[q] Bone marrow aspirate and biopsy, serum tryptase level, and additional staging studies should be performed as clinically indicated (if supported by increased symptoms and signs of progression). See Discussion.

[r] For management of midostaurin toxicity, see SM-K.

[s] For patients with advanced SM, cladribine may be particularly useful when rapid debulking of disease is required whereas [PEG]-interferon alfa, which has a cytostatic mechanism of action, may be more suitable for patients with slowly progressive disease without the need for rapid cytoreduction.

[t] See 2013 IWG-MRT-ECNM Consensus Response Criteria (SM-F). Clinical benefit may not reach the threshold of the 2013 IWG-MRT-ECNM response criteria.

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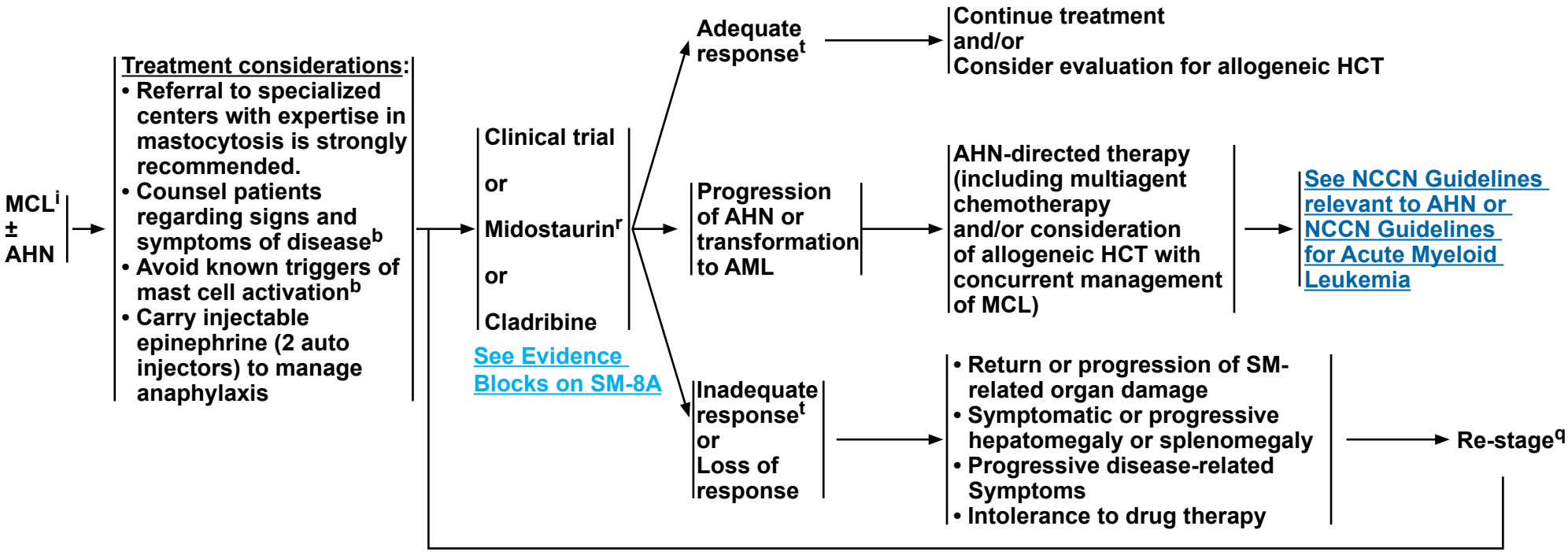
TREATMENT FOR MAST CELL LEUKEMIA[u]



[b]Patients should be counseled about the signs/symptoms and potential triggers of mast cell activation (See SM-H). Multidisciplinary collaboration with sub-specialists (eg, anesthesia for procedures/surgery; high-risk OB for pregnancy) is recommended.
[i]See 2017 Diagnostic Criteria for the Variants of Systemic Mastocytosis (SM-C).
[q]Bone marrow aspirate and biopsy, serum tryptase level, and additional staging studies should be performed as clinically indicated (if supported by increased symptoms and signs of progression). See Discussion.
[r]For management of midostaurin toxicity, see SM-K.
[t]See 2013 IWG-MRT-ECNM Consensus Response Criteria (SM-F). Clinical benefit may not reach the threshold of the 2013 IWG-MRT-ECNM response criteria.
[u]Patients with chronic MCL have no organ damage. However, treatment should be considered given the poor prognosis of MCL.

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EVIDENCE BLOCKS FOR THE TREATMENT OF SYSTEMIC MASTOCYTOSIS

Regimen	ISM or SSM[a] (SM-4)	ASM (SM-5)	SM-AHN (SM-7)	MCL (SM-8)
Cladribine				
Imatinib[b]	—		—	—
Interferon alfa-2b				—
Interferon alfa-2b + prednisone				—
Midostaurin	—			
Peginterferon alfa-2a				—
Peginterferon alfa-2a + prednisone				—
Peginterferon alfa-2b				—
Peginterferon alfa-2b + prednisone				—

[a]In patients with mast cell activation symptoms or bone disease refractory to anti mediator drug therapy or bisphosphonates.
[b]If *KIT D816V* mutation negative or unknown or if eosinophilia is present with *FIP1L1- PDGFRA* fusion gene.

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2017 WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION OF MASTOCYTOSIS[1]

1. Cutaneous mastocytosis (CM)

2. Systemic mastocytosis (SM)
- **a. Indolent systemic mastocytosis (ISM)[a]**
- **b. Smoldering systemic mastocytosis (SSM)[a]**
- **c. Systemic mastocytosis with an associated hematological neoplasm (SM-AHN)[b,c]**
- **d. Aggressive systemic mastocytosis (ASM)[a]**
- **e. Mast cell leukemia (MCL)**

3. Mast cell sarcoma (MCS)

Footnotes

[a]These subtypes require information regarding B- and C-findings for complete diagnosis, all of which may not be available at the time of initial tissue diagnosis. See WHO Criteria for B-Findings and C-Findings in Patients with Systemic Mastocytosis (SM-D).

[b]This category is equivalent to the previously described “systemic mastocytosis with an associated clonal hematological non-mast cell lineage disease (SM-AHNMD).” AHNMD and AHN can be used synonymously.

[c]The overwhelming majority of AHNs are myeloid neoplasms (e.g. MDS, MPN, MDS/MPN (e.g. chronic myelomonocytic leukemia), chronic eosinophilic leukemia (CEL), or acute myeloid leukemia (AML)). Uncommonly, lymphoid neoplasms may occur with SM (eg, chronic lymphocytic leukemia, multiple myeloma, non-hodgkin lymphomas).

References

[1]Adapted with permission from Swerdlow SH, Campo E, Harris NL, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition. IARC, Lyon, 2017.

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2017 WHO DIAGNOSTIC CRITERIA FOR CUTANEOUS AND SYSTEMIC MASTOCYTOSIS[1]

CUTANEOUS MASTOCYTOSIS (CM)

Skin lesions demonstrating the typical findings of urticaria pigmentosa (UP)/maculopapular cutaneous mastocytosis (MPCM), diffuse cutaneous mastocytosis or solitary mastocytoma, and typical histological infiltrates of mast cells in a multifocal or diffuse pattern in an adequate skin biopsy.[a] In addition, a diagnostic prerequisite for the diagnosis of CM is the absence of features/criteria sufficient to establish the diagnosis of SM.

SYSTEMIC MASTOCYTOSIS (SM)

The diagnosis of SM can be made when the major criterion and at least one minor criterion are present, or when three or more minor criteria are present.

Major criterion:

Multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s).

Minor criteria:

1. **In biopsy sections of bone marrow or other extracutaneous organs, >25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology or >25%, of all mast cells in bone marrow aspirate smears, are immature or atypical.**
2. **Detection of an activating point mutation at codon 816 of *KIT* in the bone marrow, blood, or another extracutaneous organ.**
3. **Mast cells in bone marrow, blood, or other extracutaneous organs express CD25, with or without CD2, in addition to normal mast cell markers.[b]**
4. **Serum total tryptase persistently >20 ng/ml (unless there is an associated myeloid neoplasm, in which case this parameter is not valid).**

Footnotes

[a]This criterion applies to both the dense focal and the diffuse mast cell infiltrates in the biopsy.
[b]CD25 is the more sensitive marker, by both flow cytometry and immunohistochemistry.

References

[1]Adapted with permission from Swerdlow SH, Campo E, Harris NL, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition. IARC, Lyon, 2017.

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2017 DIAGNOSTIC CRITERIA FOR THE VARIANTS OF SYSTEMIC MASTOCYTOSIS[1]

Indolent systemic mastocytosis
- Meets the general criteria for systemic mastocytosis
- No C findings[a]
- No evidence of an associated hematological neoplasm
- Low mast cell burden
- Skin lesions are frequently present

Bone marrow mastocytosis
- As above (indolent systemic mastocytosis), but with bone marrow involvement and no skin lesions

Smoldering systemic mastocytosis
- Meets the general criteria for systemic mastocytosis
- ≥2 B findings; no C findings[a]
- No evidence of an associated hematological neoplasm
- High mast cell burden
- Does not meet the criteria for mast cell leukemia

Systemic mastocytosis with an associated hematological neoplasm
- Meets the general criteria for systemic mastocytosis
- Meets the criteria for an associated hematological neoplasm (i.e. a myelodysplastic syndrome, myeloproliferative neoplasm, acute myeloid leukemia, lymphoma or another hematological neoplasm classified as a distinct entity in the WHO classification)

Aggressive systemic mastocytosis
- Meets the general criteria for systemic mastocytosis
- ≥1 C finding[a]
- Does not meet the criteria for mast cell leukemia
- Skin lesions are usually absent

Mast cell leukemia
- Meets the general criteria for systemic mastocytosis
- Bone marrow biopsy shows diffuse infiltration (usually dense) by atypical, immature mast cells
- Bone marrow aspirate smears show ≥20% mast cells
- In classic cases, mast cells account for ≥10% of the peripheral blood white blood cells, but the aleukaemic variant (in which mast cells account for <10% is more common)
- Skin lesions are usually absent

Footnotes

[a]B- and C-findings indicate organ involvement without and with organ dysfunction, respectively. See WHO Criteria for B-Findings and C-Findings in Patients with Systemic Mastocytosis (SM-D).

References

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WORLD HEALTH ORGANIZATION (WHO) CRITERIA FOR B-FINDINGS AND C-FINDINGS IN PATIENTS WITH SYSTEMIC MASTOCYTOSIS (SM)[a,1]

B-Findings: Indicate a high burden of mast cells (MCs) and expansion of the neoplastic process into multiple hematopoietic lineages, without evidence of organ damage

- **High mast cell burden (shown on bone marrow biopsy): >30% infiltration of cellularity by mast cells and (focal, dense aggregates) AND serum total tryptase >200 ng/mL.**
- **Signs of dysplasia or myeloproliferation in non-mast cell lineage(s), but criteria are not met for definitive diagnosis of an associated hematological neoplasm, with normal or only slightly abnormal blood counts.**
- **Hepatomegaly without impairment of liver function, palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging.**

C-Findings: Are indicative of organ damage produced by MC infiltration (should be confirmed by biopsy if possible)

- **Bone marrow dysfunction caused by neoplastic mast cell infiltration, manifested by ≥1 cytopenia; absolute neutrophil count <1.0 x 10^9/L, haemoglobin level <10 g/dL, and/or platelet count <100 x 10^9/L**
- **Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension**
- **Skeletal involvement, with large osteolytic lesions with or without pathologic fractures (pathological fractures caused by osteoporosis do not qualify as a C finding)**
- **Palpable splenomegaly with hypersplenism**
- **Malabsorption with weight loss due to gastrointestinal mast cell infiltrates**

Footnotes

[a]In patients with SM in whom less than 2 B-findings and no C-findings are detected (category A), the diagnosis is indolent SM (ISM). When 2 or more B-findings but no C-findings are present, the diagnosis is smoldering SM (SSM). When 1 or more C-findings (with or without additional B-findings) are detected, the final diagnosis is either ASM (<20% MCs in BM smears) or MC leukemia (MCs ≥20% on BM smears).

References

[1]Adapted with permission from Swerdlow SH, Campo E, Harris NL, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition. IARC, Lyon, 2017.

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IWG-MRT-ECNM CRITERIA FOR ELIGIBLE ORGAN DAMAGE TO ASSESS CLINICAL IMPROVEMENT (CI) AND TREATMENT RESPONSE[1]

Nonhematologic

Organ Damage	Organ Damage Eligible for CI Response	CI Response Criteria
Ascites or pleural effusions	(1) Symptomatic ascites or pleural effusion requiring medical intervention such as use of diuretics (grade 2), OR (2) ≥2 therapeutic paracenteses or thoracenteses at least 28 d apart over 12 wk prior to study entry (grade 3), and one of the procedures is performed during the 6 wk prior to drug start	(1) Complete resolution of symptomatic ascites or pleural effusion* AND no longer in need of diuretic(s) for ≥12 wk, OR (2) No therapeutic paracentesis or thoracentesis for ≥12 wk
Liver function abnormalities	≥ Grade 2 abnormalities in direct bilirubin, AST, ALT, or AP† in the presence of ascites, and/or clinically-relevant portal hypertension, and/or liver MC infiltration that is biopsy-proven or other causes for abnormal liver function are not identified	Reversion of 1 or more liver function tests to normal range for ≥12 wk
Hypoalbuminemia	≥ Grade 2 hypoalbuminemia (<3.0 g/dL)	Reversion of albumin to normal range for ≥12 wk
Symptomatic marked splenomegaly	Symptomatic marked splenomegaly: a spleen that is palpable >5 cm below the left costal margin and the patient endorses symptoms of discomfort and/or early satiety	≥50% reduction in palpable splenomegaly and no endorsement of discomfort and/or early satiety for ≥12 wk (3D computed tomography/magnetic resonance imaging evaluation may also be undertaken.)

The response criteria were determined using National Institutes of Health CTC version 4.03.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; PRBC, packed red blood cells
*Radiologic use of the term trace or minimal for ascites or pleural effusion indicates a substantial improvement of pretreatment pathologic fluid accumulation, which required medical intervention. These terms are acceptable in the absence of the radiologists' use of the term(s) complete disappearance or resolution to describe the change in ascites or effusion.
†Gamma-glutamyl transferase can be used to determine the liver vs bone origin of alkaline phosphatase but is not considered eligible as a liver-related organ damage laboratory abnormality. The grades and associated laboratory ranges above the upper limit of normal used for the total bilirubin according to CTC version 4.03 should be applied to the direct bilirubin.

[1]Gotlib J, Pardanani A, Akin C, et al. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European Competence Network on Mastocytosis (ECNM) consensus respose criteria in advanced systemic mastocytosis. Blood 2013;121(13):2393-2401.

Continued

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IWG-MRT-ECNM CRITERIA FOR ELIGIBLE ORGAN DAMAGE TO ASSESS CLINICAL IMPROVEMENT (CI) AND TREATMENT RESPONSE[1]

Hematologic

Organ Damage	Organ Damage Eligible for CI Response	CI Response Criteria
ANC	Baseline grade ≥3 ANC (<1 × 10^9/L)	A minimum 100% increase in the ANC and an ANC of at least 0.5 × 10^9/L for ≥12 wk
Anemia (transfusion-independent)	Grade ≥2 anemia (Hb <10 g/dL)	An increase in Hb level of at least 2 g/dL that is maintained for ≥12 wk
Anemia (transfusion-dependent)	Transfusion of a minimum of 6 units of PRBC in the 12 wk before the start of treatment with the most recent transfusion occurring in the previous 4 wk. RBC transfusions are only considered as part of the baseline criteria if they are administered for an Hb level ≤8.5 g/dL and not associated with bleeding, hemolysis, or therapy	Transfusion independence for ≥ 12 wk and maintenance of a minimal Hb level of 8.5 g/dL at the end of the 12 wk period of response duration
Thrombocytopenia (transfusion-independent)	Grade ≥2 thrombocytopenia (<75 × 10^9/L)	A minimum 100% increase in the platelet count and an absolute platelet count increase of at least 50 × 10^9/L and no need for platelet transfusions for ≥12 wk
Thrombocytopenia (transfusion-dependent)	1) Transfusion of a minimum of 6 units of apheresed platelets during the 12 wk preceding treatment; and 2) at least 2 units transfused in the previous 4 wk; and 3) transfusions are administered only for a platelet count <20 × 10^9/L	Transfusion-independence for a minimal period of 12 wk and maintenance of a platelet count of ≥20 × 10^9/L

[1]Gotlib J, Pardanani A, Akin C, et al. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European Competence Network on Mastocytosis (ECNM) consensus respose criteria in advanced systemic mastocytosis. Blood 2013;121(13):2393-2401.

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IWG-MRT-ECNM CONSENSUS RESPONSE CRITERIA FOR PATIENTS WITH ASM, MCL, AND SM ASSOCIATED WITH A MYELOID NEOPLASM[1]

Complete remission (CR)*
Requires all 4 criteria and response duration must be ≥12 wk
- **No presence of compact neoplastic mast cell aggregates in the BM or other biopsied extracutaneous organ**
- **Serum tryptase level <20 ng/mL†**
- **Peripheral blood count remission defined as ANC ≥1 x 10^9/L with normal differential, Hb level ≥11 g/dL, and platelet count ≥100 x 10^9/L**
- **Complete resolution of palpable hepatosplenomegaly and all biopsy-proven or suspected SM-related organ damage (CI findings)‡**

Partial remission (PR)*
Requires all 3 criteria and response duration must be ≥12 wk, in the absence of both CR and progressive disease (PD)
- **Reduction by ≥50% in neoplastic MCs in the marrow and/or or other extracutaneous organ at biopsy demonstrating eligible SM-related organ damage**
- **Reduction of serum tryptase level by ≥50%†**
- **Resolution of 1 or more biopsy-proven or suspected SM-related organ damage (CI finding(s))‡**

Clinical improvement (CI)*
Response duration must be ≥12 wk
- **Requires 1 or more of the nonhematologic and/or hematologic response criteria to be fulfilled (see Table 3) in the absence of both CR/PR assignment or progressive disease (PD)**

Stable disease (SD)
Not meeting criteria for CR, PR, CI, or PD (Continued)

Guidelines for adjudicating response are as follows: (1) Only disease-related ≥ grade 2 organ damage is evaluable as a primary endpoint in clinical trials. (2) Response adjudications of CR, PR, SD, PD, and LOR should only be applied to these ≥ grade 2 organ damage findings in the context of trials. (3) Disease status at the time of patient removal from the study singularly relates to the updated status of initial ≥ grade 2 organ damage finding(s). (4) Exclusion of drug-related toxicity and/or other clinical issues (eg, gastrointestinal tract bleeding in the case of worsening anemia/transfusion-dependence) should be undertaken before assigning the designation PD or LOR in a patient with worsening of baseline ≥ grade 2 organ damage.

*Responses that are not maintained or confirmed for a period of at least 12 wk do not fulfill criteria for CR, PR, or CI; however, both maintained and unmaintained (<12-wk duration) responses in organ damage should be recorded to determine median duration of response.

†Only valid as a response criterion if the pretreatment serum tryptase level is ≥ 40 ng/mL.

‡Biopsy of organ(s) in addition to the BM to evaluate for SM-related organ damage may be considered.

[1]Gotlib J, Pardanani A, Akin C, et al. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European Competence Network on Mastocytosis (ECNM) consensus respose criteria in advanced systemic mastocytosis. Blood 2013;121(13):2393-2401.

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IWG-MRT-ECNM CONSENSUS RESPONSE CRITERIA FOR PATIENTS WITH ASM, MCL, AND SM ASSOCIATED WITH A MYELOID NEOPLASM[1]

Progressive disease (PD)[§]

Requires at least 1 element of either criteria 1 or 2 and duration must be ≥8 weeks

(1) For patients with baseline grade 2 nonhematologic organ damage:
- **a) worsening by 1 grade, AND**
- **b) minimum 100% increase (doubling) of laboratory abnormality**

For patients with baseline ≥ grade 2 albumin:
- **(a) worsening by 1 grade, AND**
- **(b) decrease by ≥0.5 g/dL**

For patients with baseline ≥ grade 3 nonhematologic organ damage: minimum 100% increase (doubling) of laboratory abnormality

For patients with baseline ≥ grade 2 transfusion-independent anemia or thrombocytopenia: New transfusion dependence of ≥ 4 units of RBCs 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:
- **(a) >50% decrease in neutrophil count, AND**
- **(b) absolute decrease of neutrophil count of ≥250/mm^3, AND**
- **(c) grade 4**

(2) 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 week. 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 week. The baseline value for LOR is the pretreatment measurement(s) and not the nadir values during response.

Guidelines for adjudicating response are as follows: (1) Only disease-related ≥ grade 2 organ damage is evaluable as a primary endpoint in clinical trials. (2) Response adjudications of CR, PR, SD, PD, and LOR should only be applied to these ≥ grade 2 organ damage findings in the context of trials. (3) Disease status at the time of patient removal from the study singularly relates to the updated status of initial ≥ grade 2 organ damage finding(s). (4) Exclusion of drug-related toxicity and/or other clinical issues (eg, gastrointestinal tract bleeding in the case of worsening anemia/transfusion-dependence) should be undertaken before assigning the designation PD or LOR in a patient with worsening of baseline ≥ grade 2 organ damage.

[§]Preservation of at least one CI finding permits a patient to maintain the response of 'CI' if 1 or more CI findings are lost but none meet criteria for progressive disease (PD). However, if 1 or more of the CI findings become PD, then the CI finding assignment is lost and the patient meets criteria for PD. The baseline value for evaluating PD is the pretreatment measurement(s). The PD findings must be considered related to the underlying disease and not to other clinical factors. Progression of an underlying chronic myeloid neoplasm to AML is also considered PD in the setting of clinical trials.

[¶]For clinical trials using 3D computed tomography or magnetic resonance imaging as an additional modality to quantify organomegaly, progression in splenomegaly is defined as an increase in spleen volume of at least 25%.

[1]Gotlib J, Pardanani A, Akin C, et al. International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European Competence Network on Mastocytosis (ECNM) consensus respose criteria in advanced systemic mastocytosis. Blood 2013;121(13):2393-2401.

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RECOMMENDATIONS FOR HISTOPATHOLOGY ANALYSIS

- **Review of the bone marrow or other extracutaneous organ(s) for involvement by neoplastic mast cells should be undertaken by a hematopathologist and/or center with expertise in the management of patients with mast cell diseases.**
- **The peripheral blood smear should be reviewed for the presence of mast cells (eg, mast cell leukemia) and/or for evidence of an associated hematologic neoplasm (AHN; eg, dysplasia, monocytosis, and/or eosinophilia). The percentage of circulating mast cells should be reported in patients with mast cell leukemia (eg, ≥10% vs. <10% mast cells [aleukemic variant]).**
- **Bone marrow aspirate analysis should include comment on the percentage of neoplastic mast cells, and their morphology (spindle-shaped, well-differentiated [resembling normal mast cells], and immature [eg, promastocytes with indented or bilobed nuclei or metachromatic blasts]). The percentage of abnormal mast cells out of total mast cells should be determined. The aspirate should also be reviewed for features of an AHN.**
- **Bone marrow core biopsy analysis should include comment on the mast cell burden, and whether mast cells form multifocal dense infiltrates (a major diagnostic criterion) or a primarily interstitial pattern of involvement. In cases with a primarily interstitial pattern of mast cells, peripheral blood eosinophilia, and negativity for KIT D816V mutation, then the FIP1L1-PDGFRA fusion gene should be tested.**
- **On the core biopsy, immunohistochemistry with markers for mast cell tryptase, CD117, and CD25 should be performed to optimize quantification of the bone marrow biopsy mast cell burden. Cytoplasmic and/or surface expression of CD30 may be found on mast cells, especially in advanced disease, but is considered an optional immunohistochemical marker; this can be helpful in cases where CD25 is negative. CD34 staining may also be obtained to quantify whether the proportion of myeloblasts are increased, especially in SM-AHN cases, eg, SM associated with MDS, MPN, MDS/MPN, CEL, NOS, or AML.**
- **Reticulin and collagen staining should also be undertaken to assess the grade of bone marrow fibrosis (eg, MF-0 to MF-3), which is relatively common in advanced SM, particularly in areas of mast cell aggregates.**
- **Flow cytometry is a complementary tool in the diagnosis or monitoring of mast cell disease. CD117, CD25, and CD2 are standard flow markers; testing for CD30 can also be considered. Flow cytometric characterization of mast cells comprises rare event analyses; optimal techniques for characterization and enumeration of neoplastic mast cells are described in the literature.[1-3]**
- **Chromosome analysis should be obtained in the workup of systemic mastocytosis, especially in cases with a suspected AHN.**
- **Myeloid mutation panel testing should be performed on the bone marrow, but can be performed on the peripheral blood in the presence of an AHN and/or circulating mast cells. Myeloid mutation panels are not recommended for the detection of KIT D816V; such next-generation sequencing (NGS) assays exhibit low sensitivity of approximately 5%.**

[1]Escribano L, Garcia Montero AC, Nunez R, et al. Flow cytometric analysis of normal and neoplastic mast cells: role in diagnosis and follow-up of mast cell disease. Immunol Allergy Clin North Am 2006;26:535-547.
[2]Sánchez-Muñoz L, Teodosio C, Morgado JM, et al. Flow cytometry in mastocytosis: utility as a diagnostic and prognostic tool. Immunol Allergy Clin North Am 2014;34:297-313.
[3]Teodosio C, Mayado A, Sánchez-Muñoz L, et al. The immunophenotype of mast cells and its utility in the diagnostic work-up of systemic mastocytosis J Leukoc Biol 2015;97:49-59.

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RECOMMENDATIONS FOR KIT D816V MUTATION TESTING IN SYSTEMIC MASTOCYTOSIS[4]

- **If a diagnosis of SM is suspected, use of a highly sensitive assay such as allele-specific oligonucleotide quantitative reverse transcriptase polymerase chain reaction (ASO-qPCR) can first be undertaken on the peripheral blood, in combination with measurement of the serum tryptase level and evaluation of clinical signs and/or symptoms suggestive of SM-related organ involvement.**
- **Following a positive test on peripheral blood, KIT mutational analysis may also be performed on the bone marrow aspirate; this can be performed on formalin-fixed paraffin-embedded tissue if this tissue has not been decalcified, or has been decalcified in EDTA. Other fixatives and rapid decalcification will yield unsatisfactory results. If initial screening of the peripheral blood fails to detect the KIT D816V mutation in a patient with suspected SM, testing of the bone marrow should be undertaken.**
- **When applied to the bone marrow, these assays can detect the KIT D816V mutation in >80% of patients with SM, a sensitivity that is considered sufficient in daily practice for routine diagnostic screening of SM. In cases of a suboptimal bone marrow aspirate (eg, dry tap), testing of the peripheral blood should be undertaken as an alternative option for detection of KIT D816V mutation.**
- **In <5%–10% of patients, no KIT D816V mutation is detected. This may be due to: 1) patients are in fact KIT D816V positive, but the (very) low mast cell burden leads to a false-negative result because the sensitivity of the applied assay is too low and/or the tissue sample is suboptimal; 2) patients indeed only bear wild-type KIT; or 3) patients are positive for other mutations at codon 816 (D816H, D816Y, others) or in other regions of KIT that are not detectable by the ASO-qPCR assays for KIT D816V mutation. In patients with low mast cell burden ISM who are otherwise negative for KIT D816V mutation, evaluation for KIT D816V mutation in the skin or from an extracutaneous organ besides the bone marrow could be considered.**
- **In patients with a high mast cell burden and a negative KIT D816V screen, the result should be confirmed with the most sensitive technique available, ASO-qPCR, if not originally obtained with this technique. If KIT D816V mutation is still negative, this should be followed by evaluation of KIT for alternative codon 816 mutations, which requires amplification of codon 17 and sequencing of the resulting amplicons, or preferably peptide nucleic acid (PNA)-mediated PCR.**
- **If no mutation is found at codon 816, sequencing of the whole KIT coding sequence by next-generation sequencing (NGS) may be undertaken. However, the sensitivity of myeloid gene mutation panels for detection of KIT mutations is relatively lower, at ~5%.**
- **In patients with low mast cell burden ISM and a stable, clinical course, evaluation of KIT D816V allele burden (if available) should be considered at diagnosis, but should not necessarily be repeated, unless signs of disease progression occur.**
- **In patients with more aggressive forms of SM, and those enrolled in clinical trials involving cytoreductive therapies, evaluation of KIT D816V allele burden (if available) by sensitive ASO-qPCR on DNA or on RNA/cDNA should be considered before initiating therapy and serially during therapy.**

[4]Arock M, Sotlar K, Akin C, et al. KIT mutation analysis in mast cell neoplasms: recommendations of the European Competence Network on Mastocytosis. Leukemia. 2015;29(6):1223-1232.

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ADVERSE PROGNOSTIC VARIABLES IN SYSTEMIC MASTOCYTOSIS

Clinical/Laboratory Variables

- **WHO subclassification of SM[5]**
- **Advanced age, history of weight loss, anemia, thrombocytopenia, hypoalbuminemia, and excess bone marrow blasts (>5%)[5]**
- **Eosinophilia[6,a]**
- **Splenomegaly[7]**
- **Increased alkaline phosphatase[7]**

Cytogenetic/Molecular Variable

- **Poor-risk karyotype (monosomy 7 or complex karyotype)[8]**
- **Multilineage involvement of *KIT* D816V mutation[9]**
- ***SRSF2/ASXL1/RUNX1* (S/A/R) or *ASXL1/CBL* mutation profile[7,8,10,11,12]**
- **Number of non-*KIT* D816V mutations[10]**

Footnotes

[a]Patients who are KIT D816V mutation negative or who exhibit eosinophilia with the FIP1L1-PDGFRA fusion gene have a good prognosis.

References

[5]Lim KH, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood 2009;113:5727-5736.
[6]Bohm A, Födinger M, Wimazal F, et al. Eosinophilia in systemic mastocytosis: clinical and molecular correlates and prognostic significance J Allergy Clin Immunol 2007;120:192-199.
[7]Jawhar M, Schwaab J, Hausmann D,et al. Splenomegaly, elevated alkaline phosphatase and mutations in the SRSF2/ASXL1/RUNX1 gene panel are strong adverse prognostic markers in patients with systemic mastocytosis. Leukemia 2016;30:2342-2350.
[8]Naumann N, Jawhar M, Schwaab J, et al. Incidence and prognostic impact of cytogenetic aberrations in patients with systemic mastocytosis. Genes Chromosomes Cancer 2018;57(5)252-259.
[9]Garcia-Montero AC, Jara-Acevedo M, Teodosio C, et al. KIT mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: a prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. Blood 2006;108:2366-2372.
[10]Schwaab J, Schnittger S, Sotlar K, et al. Comprehensive mutational profiling in advanced systemic mastocytosis. Blood 2013;122:2460-2466.
[11]Jawhar M, Schwaab J, Schnittger S, et al. Additional mutations in SRSF2, ASXL1 and/or RUNX1 identify a high-risk group of patients with KIT D816V(+) advanced systemic mastocytosis. Leukemia 2016;30:136-143.
[12]Pardanani AD, Lasho TL, Finke C, et al. ASXL1 and CBL mutations are independently predictive of inferior survival in advanced systemic mastocytosis. Br J Haematol 2016;175:534-536.

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SIGNS AND SYMPTOMS OF MAST CELL ACTIVATION[a,b]

- Anaphylaxis
- Flushing of the face, neck, and chest
- Pruritus, itching, +/- rash
- Hives, skin rashes
- Angioedema (swelling)
- Nasal itching and congestion
- Wheezing and shortness of breath
- Throat itching and swelling
- Headache and/or brain fog, cognitive dysfunction, anxiety, depression
- Gastric distress, diarrhea, nausea, vomiting, abdominal pain, bloating, gastroesophageal reflux disease (GERD)
- Bone/muscle pain, osteosclerosis, osteopenia, osteoporosis
- Light-headedness, syncope/fainting
- Rapid heart rate, chest pain
- Low blood pressure, high blood pressure at the start of a reaction, blood pressure instability
- Fatigue
- Neuropsychiatric symptoms

POTENTIAL TRIGGERS OF MAST CELL ACTIVATION

- Heat, cold, or sudden temperature changes
- Stress: emotional, physical, including pain, or environmental (eg, weather changes, pollution, pollen, pet dander)
- Exercise
- Food or beverages, including alcohol
- Drugs (opioids, NSAIDs, antibiotics, and some local/systemic anesthetics) and contrast dyes
- Natural odors, chemical odors, perfumes, and scents
- Insect stings
- Venoms (eg, bee, wasp, mixed vespids, spiders, fire ants, jelly fish, snakes)
- Infections (viral, bacterial, or fungal)
- Mechanical irritation, friction, or vibration
- Sun/sunlight
- Lack of sleep/sleep deprivation
- Surgery
- Vaccinations
- Procedures (eg, endoscopy, colonoscopy)

[a]Specific criteria have been established for primary and secondary MCAS (Akin C. Mast cell activation syndromes. J Allergy Clin Immunol 2017;140:349-355). Primary MCAS has also been referred to as monoclonal mast cell activation syndrome (MMAS). (See Discussion).
[b]From The Mastocytosis Society website: https://tmsforacure.org/symptoms/symptoms-and-triggers-of-mast-cell-activation/

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ANTI-MEDIATOR DRUG THERAPY APPROACHES FOR MAST CELL ACTIVATION SYMPTOMS[a]

Avoidance of Triggers

- Specific foods, medications, allergens, and general triggers
- Physical measures
  - Avoid sudden changes in temperature
  - Avoid extreme temperatures in bath/shower, swimming pool, air conditioning
  - Avoid dryness of skin
  - Avoid rubbing

Skin Care

- Take steps to avoid dryness of skin
- Use skin moisturizer
  - Water-soluble sodium cromolyn cream: apply two to four times a day for urticaria, pruritus, vesicles, or bullae. Do not use on denuded lesions (consider topical antibiotics).
  - Topical corticosteroids and cream
  - Diffuse lesions: apply bath or sterile gauze with zinc sulfate

Solitary Mastocytoma

- Water-soluble sodium cromolyn cream
- Corticosteroid cream
- Avoid friction and pressure
- Consider surgical excision (ie, flexures, soles, palms, scalp)

Urticaria Pigmentosa and Other Forms

- Trigger(s)-related symptoms
  - Avoidance of triggers
  - H1 antihistamines
  - H2 antihistamines

- Continuous moderate symptoms
  - Scheduled non-sedating H1 antihistamines; add sedating H1 antihistamines on demand
  - Scheduled or on-demand H2 antihistamines
  - Oral disodium cromolyn in case of persistent symptoms

- Severe symptoms
  - Scheduled non-sedating H1 antihistamines
  - Scheduled sedating H1 antihistamines
  - Scheduled H2 antihistamines
  - Oral disodium cromolyn
  - Add anti-leukotrienes in refractory cases

Diffuse Forms with Life-threatening Mast Cell-mediated Related Symptoms, Bullae, and Blistering

- Treatment may require hospitalization
- Sterile conditions
- Topical sodium cromolyn
- Topical corticosteroids
- Zinc sulfate

[a]Specific criteria have been established for primary and secondary MCAS (Akin C. Mast cell activation syndromes. J Allergy Clin Immunol 2017;140:349-355). Primary MCAS has also been referred to as monoclonal mast cell activation syndrome (MMAS). (See Discussion).

Continued

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STEPWISE PROPHYLACTIC TREATMENT APPROACH FOR CHRONIC MAST CELL MEDIATOR-RELATED SYMPTOMS

Organ Involvement/Symptoms	Stepwise Treatment[b,c]
Skin: **Pruritus, flushing, urticaria, angioedema dermatographism**	**1. H1 blockers and H2 blockers** **2. Leukotriene receptor antagonist** **3. Aspirin** **4. Ketotifen[d]** **5. 4% Cromolyn sodium cream/ointment**
Gastrointestinal: **Diarrhea, abdominal cramping, nausea, vomiting**	**1. H2 blockers** **2. Cromolyn sodium** **3. Proton pump inhibitors** **4. Leukotriene receptor antagonist** **5. Ketotifen[d]**
Neurologic: **Headache, poor concentration and memory, brain fog**	**1. H1 blockers and H2 blockers** **2. Cromolyn sodium** **3. Aspirin** **4. Ketotifen[d]**
Cardiovascular: **Pre-syncope, tachycardia**	**1. H1 blockers and H2 blockers** **2. Corticosteroids** **3. Omalizumab**
Pulmonary: **Wheezing, throat Swelling**	**1. H1 blockers and H2 blockers** **2. Corticosteroids** **3. Omalizumab**
Naso-ocular: **Nasal stuffiness, nasal pruritus, conjunctival injection**	**1. H1 blockers** **2. Corticosteroids** **3. Cromolyn sodium**

[b]Standard doses need to be titrated. Higher doses may be necessary for symptoms refractory to standard-dose treatment.
[c]The use of these medications in a stepwise treatment plan may vary according to the specific patient scenarios.
[d]Available as a compounded agent.

Continued

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ACUTE TREATMENT OF ANAPHYLAXIS[1-7]
(Includes hymenoptera venom anaphylaxis)

Indication	Treatment
Systemic hives	Anti-histamines (H1 blockers and H2 blockers)
Systemic hives + second organ involved in an acute onset reaction (eg, upper/lower airway, gastrointestinal, neurologic, cardiovascular)	Epinephrine intramuscular (can be repeated 3 times every 5 minutes)
Acute onset of anaphylaxis with the following symptoms: • Hypotension • Laryngeal edema • Vasomotor collapse • Oxygen desaturation • Seizures	Epinephrine intramuscular (can be repeated 3 times every 5 minutes)
Complementary Treatments (in addition to antihistamines) • IV fluids • Oxygen • Corticosteroids (0.5–1 mg/kg) • Consider Glucagon (if anaphylaxis related to B-blockade) • Consider bradykinin inhibitor (if anaphylaxis due to ACE inhibitor)	

PREVENTION OF ANAPHYLAXIS[1-7]

Indication	Treatment
• Hymenoptera-specific IgE or skin test positive	Venom immunotherapy Rush desensitization (may be available only in selected centers)
• Unprovoked anaphylaxis • Hymenoptera or food-induced, with negative specific IgE or negative skin test • To improve tolerance while on immunotherapy	Omalizumab

Continued

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TREATMENT FOR OSTEOPENIA/OSTEOPOROSIS[8,9]

- **Supplemental calcium and vitamin D**
- **Bisphosphonates (with continued use of antihistamines)**
  - **May resolve bone pain and improve vertebral bone mineral density (more than femoral head bone mineral density)**
- **[PEG]-Interferon-alfa**
  - **Consider for patients with refractory bone pain and/or worsening bone mineral density on bisphosphonate therapy**
- **Anti-RANKL monoclonal antibody (eg, denosumab)**
  - **Generally used as second-line therapy for patients with bone pain not responding to bisphosphonates or for patients who are not candidates for bisphophonates because of renal insufficiency**
- **Vertebroplasty/kyphoplasty for refractory pain associated with vertebral compression fractures in selected patients**

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SPECIAL CONSIDERATIONS FOR THE MANAGEMENT OF PATIENTS WITH SYSTEMIC MASTOCYTOSIS

Surgery[1-4]

- Risk of anaphylaxis in the perioperative period is estimated to be higher in patients with SM relative to the the general population, but anesthesia is not contraindicated in patients with SM.
- Multidisciplinary management is recommended with the involvement of surgical, anesthesia, and perioperative medical teams.
- Mast cell activation can occur from IgE-related or IgE-unrelated mechanisms. The primary goal of management is to prevent mast cell activation during and in the immediate aftermath of the surgical procedure.
- Careful review of prior anesthetic records and identification/avoidance of known triggers of mast cell activation are critical.
- Temperature extremes (hypothermia or hyperthermia) and unnecessary trauma (eg, with patient positioning) that could lead to mast cell activation symptoms, skin blistering, or osteolytic fractures should be avoided in the operating room.
- Pre-anesthetic treatment is probably helpful in reducing the frequency and/or severity of mast cell activation events. This includes the use of anxiolytic agents (eg, benzodiazepines), antihistamines (H1 and H2 blockers), and possibly corticosteroids, which can help in resolution of mast cell activation symptoms.
- Certain perioperative drugs are considered safer, although the supporting data are anecdotal and not evidence based. These include certain anesthetic induction (propofol) or inhalational (sevoflurane or isoflurane) agents, analgesics (fentanyl or remifentanil), local anesthetics (lidocaine, bupivacaine), and skin antiseptics (povidone isodine).
- Agents to be avoided include the muscle relaxants atracurium and mivacurium (rocuronium and vecuronium may be safer) and succinylcholine. While caution should be exercised with opiates (eg, codeine or morphine), it is important, however, that analgesics not be withheld from patients with SM since pain can be a trigger for mast cell activation.
- Management of mast cell activation symptoms depends upon their severity, and relies upon discontinuation of the suspected drug or anesthetic agent, fluid resuscitation, and intravenous epinephrine for severe reactions. Corticosteroids and antihistamines (H1 and H2 blockers) may be used as adjuncts.
- In the event of anaphylaxis or other mast cell activation event, a full allergic workup should be initiated. Serum tryptase level should be checked within 30–120 minutes of onset of symptoms. Measurement of baseline serum tryptase level after full recovery is an important comparator. Identification of IgE-mediated hypersensitivity to drugs or latex requires detection of specific IgE and skin testing (skin prick and intradermal tests).

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SPECIAL CONSIDERATIONS FOR THE MANAGEMENT OF PATIENTS WITH SYSTEMIC MASTOCYTOSIS

Pregnancy[5-12]

- **Based on a paucity of studies, insufficient evidence currently exists regarding whether a diagnosis of SM results in significantly increased rates of adverse maternal or fetal outcomes (eg, spontaneous miscarriage, preterm infants, complications of labor and delivery) compared to the general population.**
- **A diagnosis of SM does not appear to affect fertility.**
- **Pre-conception, pregnancy, and the peripartum period should be managed by a multidisciplinary team, including high-risk obstetrics, anesthesia, and allergy.**
- **Management of SM during pregnancy involves alleviation of symptoms related to mast cell activation and titration of acceptable medications to minimize potential harm to the fetus.**
- **Avoidance of triggers, prophylactic use of antihistamines, as-needed corticosteroids, and epinephrine on demand for anaphylaxis are standard approaches during pregnancy. Please refer to the table for medications used to treat mastocytosis and their potential risks during both pregnancy and lactation (SM-J 3 of 4).**
- **For severe cases of SM during pregnancy refractory to conventional therapy, cytoreductive therapy with interferon-alfa can be considered. Use of cladribine or tyrosine kinase inhbitors (eg, imatinib, midostaurin) is not recommended.**

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SPECIAL CONSIDERATIONS FOR THE MANAGEMENT OF PATIENTS WITH SYSTEMIC MASTOCYTOSIS

Table 1. Mastocytosis Treatments and Pregnancy / Lactation Risk[a]

Group	Medication	Risk Category	Pregnancy Implication	Lactation Implications
First-generation H1 antihistamines	Brompheniramine	C	Increased risk of birth defects	Use with caution
	Chlorpheniramine	C	No increased risk of birth defects	Excreted in breast milk, use with caution
	Dimenhydrinate	B	Crosses placenta, no increased risk of fetal abnormalities	Excreted in breast milk, use with caution
	Diphenhydramine	B	Cross placenta, unclear historical association with cleft palate	Excreted in breast milk, breastfeeding contraindicated
	Doxylamine	C	Historical association with neural tube defects, oral clefts, hypoplastic left heart	Breastfeeding contraindicated
	Hydroxyzine	Not assigned	Crosses placenta, no increased risk of birth defects but not recommended in early pregnancy	Breastfeeding not recommended
	Meclizine	B	No increased risk of birth defects	Unknown if excreted into breast milk
Second-generation H1 antihistamines	Cetirizine	B	No increased risk of birth defects	Excreted in breast milk
	Levocetirizine	B	No increased risk of birth defects	Unknown if excreted into breast milk, not recommended
	Loratadine	B	No increased risk of birth defects, prior historical association with hypospadias	Small amounts excreted into breast milk
	Fexofenadine	C	Limited information available	Excreted in breast milk
	Desloratadine	C	Adverse side effects in animal studies	Excreted in breast milk
H2 antihistamines	Cimetidine	B	Crosses placenta, no increased risk of birth defects	Excreted in breast milk, breastfeeding not recommended
	Famotidine	B	Crosses placenta, no increased risk of birth defects	Excreted in breast milk, use with caution
	Ranitidine	B	Crosses placenta, no increased risk of birth defects	Excreted in breast milk, use with caution
Mast cell stabilizer	Cromolyn	B	Safe in pregnancy	No data on excretion into breast milk, use with caution
	Ketotifen	C	Adverse events in animal studies	Breastfeeding not recommended
Anti-IgE antibody	Omalizumab	B	No increased risk of birth defects	Likely excreted in breast milk, not recommended

Category A: The safest drugs to take during pregnancy. No known adverse reactions.
Category B: No risks have been found in humans.
Category C: Not enough research has been done to determine if these drugs are safe.
Category D: Adverse reactions have been found in humans.

[a]Breastfeeding by patients with SM should be done in consultation with a pediatrician and International Board Certified Lactation Consultant (IBCLC).

Continued

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SPECIAL CONSIDERATIONS FOR THE MANAGEMENT OF PATIENTS WITH SYSTEMIC MASTOCYTOSIS

Table 1. (continued) Mastocytosis Treatments and Pregnancy / Lactation Risk[a]

Group	Medication	Risk Category	Pregnancy Implications	Lactation Implications
Glucocorticoids	Hydrocortisone	C	Increased risk of oral clefts with use in the first trimester	Excreted in breast milk, wait 4 h after dose
	Prednisone	C/D	Increased risk of oral clefts with use in the first trimester	Excreted in breast milk
	Betamethasone	C	Increased risk of oral clefts with use in the first trimester, nonfluorinated corticosteroid preferred	Excreted in breast milk, wait 4 h after dose
	Dexamethasone	C	Increased risk of oral clefts with use in the first trimester, nonfluorinated corticosteroid preferred	Excreted in breast milk, wait 4 h after dose
Leukotriene receptor antagonist	Montelukast	B	No increased risk of birth defects	Unknown if excreted into breast milk, use with caution
Cytoreductive therapies	Cladribine	D	Teratogenic effects and fetal mortality observed	Not recommended
	Imatinib	D	Pregnancy not recommended (in mother or father) within 2 wk of last imatinib dose	Not recommended
	Interferon alpha-2b	C	No clear association, contraindicated in combination therapy with ribavirin	Excreted in breast milk

Category A: The safest drugs to take during pregnancy. No known adverse reactions.
Category B: No risks have been found in humans.
Category C: Not enough research has been done to determine if these drugs are safe.
Category D: Adverse reactions have been found in humans.

[a]Breastfeeding by patients with SM should be done in consultation with a pediatrician and International Board Certified Lactation Consultant (IBCLC).

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MANAGEMENT OF MIDOSTAURIN TOXICITY[1]

- **The starting dose of midostaurin is 100 mg twice daily with food.**
- **Co-administration of midostaurin with strong CYP3A inhibitors may increase midostaurin concentrations. Consider alternative concomitant therapies that do not strongly inhibit CYP3A activity.**

Hematologic Toxicities:
- **ANC <1 x 10^9/L attributed to midostaurin in patients without MCL, or ANC <0.5 x 10^9/L attributed to midostaurin in patients with baseline ANC value of 0.5–1.5 x 10^9/L: Interrupt midostaurin until ANC >1 x 10^9/L, then resume midostaurin at 50 mg twice daily, and if tolerated, increase to 100 mg twice daily. Discontinue midostaurin if low ANC persists for >21 days and is suspected to be related to midostaurin.**
- **Platelet count <50 x 10^9/L attributed to midostaurin in patients without MCL, or platelet count <25 x 10^9/L attributed to midostaurin in patients with baseline platelet count of 25–75 x 10^9/L: Interrupt midostaurin until platelet count >50 x 10^9/L, then resume midostaurin at 50 mg twice daily, and if tolerated, increase to 100 mg twice daily. Discontinue if low platelet count persists for >21 days and is suspected to be related to midostaurin.**
- **Hemoglobin <8 g/dL attributed to midostaurin in patients without MCL, or life-threatening anemia attributed to midostaurin in patients with baseline hemoglobin value of 8–10 g/dL. Interrupt midostaurin until hemoglobin >8 g/dL, then resume midostaurin at 50 mg twice daily, and if tolerated, increase to 100 mg twice daily. Discontinue if low hemoglobin persists for >21 days and is suspected to be related to midostaurin.**

Non-Hematologic Toxicities:
- **Grade 3/4 nausea and/or vomiting despite optimal antiemetic therapy: Interrupt midostaurin for 3 days (6 doses), then resume midostaurin at 50 mg twice daily, and if tolerated, increase to 100 mg twice daily.**
- **Other grade 3/4 non-hematologic toxicities: Interrupt midostaurin until event has resolved to ≤ grade 2, then resume midostaurin at 50 mg twice daily, and if tolerated, increase to 100 mg twice daily.**

Rare But Serious Toxicities:
- **Cases of interstitial lung disease and pneumonitis, some fatal, have occurred in patients treated with midostaurin as monotherapy or with chemotherapy. Monitor patients for pulmonary symptoms. Discontinue midostaurin in patients who experience signs or symptoms of interstitial lung disease or pneumonitis without an infectious etiology.**

Specific Interventions:
- **GI upset: Administer prophylactic antiemetics (eg, ondanestron or granisetron) 1 hour before treatment with midostaurin to reduce the risk of nausea and vomiting. Take doses with food.**

[1]Please refer to package insert for full prescribing information and monitoring of hematologic or biochemical abnormalities, available at www.fda.gov.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

Table of Contents

Overview

Mastocytosis is a group of heterogeneous disorders resulting from the clonal proliferation of abnormal mast cells and their accumulation in the skin and/or in various extracutaneous organs.[1] In the revised 2017 WHO classification, mastocytosis was removed as one of the subtypes of myeloproliferative neoplasms (MPN) and listed as a separate major disease entity with its distinctive clinical and pathologic features.[2] Mastocytosis is divided into three broad subtypes, depending on the pathology, distribution of disease, and clinical manifestations. Cutaneous mastocytosis (CM) is limited to the skin and is most commonly diagnosed in children. Systemic mastocytosis (SM) is the most common form of mastocytosis diagnosed in adults, characterized by mast cell infiltration of one or more extracutaneous organs (with or without skin involvement). Mast cell sarcoma, defined as a malignant mast cell neoplasm presenting as a solitary destructive mass, is extremely rare in humans.[3]

The management of patients with mastocytosis requires a multidisciplinary team approach (involving dermatologists, hematologists, gastroenterologists, pathologists, and allergists/immunologists) preferably in specialized medical centers with expertise in the treatment of patients with mast cell disorders.[4,5] The identification of *KIT* D816V mutation and the emergence of novel targeted therapies have significantly improved the diagnosis and treatment of SM.[6,7] However, certain aspects of clinical care, particularly the diagnosis, assessment and management of mediator-related symptoms continue to present challenges.

The NCCN Guidelines provide recommendations for the diagnosis and management of patients with SM. Management of CM is not included in these guidelines. Referral to centers with expertise in CM is strongly recommended.

Literature Search Criteria and Guidelines Update Methodology

Prior to the development of NCCN Guidelines® for Systemic mastocytosis, an electronic search of the PubMed database was performed to obtain key literature in Systemic mastocytosis published in the last 10 years, using the following search terms: mastocytosis, systemic mastocytosis. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[8]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles selected by the panel for review during the Guidelines panel meeting as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

Diagnostic Classification

Cutaneous Mastocytosis

The diagnosis of CM requires the presence of clinical and histopathological findings of abnormal mast cell infiltration of the dermis with no evidence of systemic mast cell infiltration either in the bone marrow or other extracutaneous organs.[2] CM is further subdivided into three different sub-variants: Urticaria pigmentosa (UP)/maculopapular cutaneous mastocytosis (MPCM), diffuse CM, and mastocytoma of the skin.[9]

Systemic Mastocytosis

The WHO diagnostic criteria include one major diagnostic criterion (multifocal, dense infiltrates of mast cells [≥15 mast cells in aggregates] detected in the biopsy sections of bone marrow and/or other extracutaneous organs) and four minor diagnostic criteria (the presence of atypical mast cells in lesional tissues; the presence of *KIT* D816V mutation; the aberrant expression of CD25 with or without CD2 on neoplastic mast cells, and a persistently elevated serum tryptase level [> 20 ng/mL]).[2]

The diagnosis of SM is established when one major criterion and at least one minor criterion are present, or when at least three minor criteria are present. SM is further divided into 5 different subvariants (based on the mast cell burden, organ involvement, and SM-related organ damage).

- Indolent SM (ISM)
- Smoldering SM (SSM)
- Aggressive SM (ASM)
- SM with an associated hematological neoplasm (SM-AHN)
- Mast Cell Leukemia (MCL)

This subclassification has been validated in a number of studies.[10-12] The diagnostic criteria for variants of systemic mastocytosis are outlined in MS-5.

Well-differentiated SM (WDSM) is a rare variant characterized by bone marrow infiltration of round, rather than spindle-shaped mast cells often lacking *KIT* D816V mutation and low or absent CD25 expression.[13] WDSM is not a WHO-defined variant, but rather is a morphologic variant that exists across the spectrum of WHO-defined subtypes of both ISM and advanced SM.

Mast Cell Activation Syndrome

Mast cell activation syndrome (MCAS), refers to a group of disorders associated with episodic symptoms related to mast cell mediator release. MCAS is not considered a subtype of SM. MCAS is not associated with an over proliferation of cells and is not considered a pre-diagnostic condition that ultimately progresses to SM. MCAS can be divided into primary, secondary, and idiopathic. Basic defining criteria of MCAS include: 1) episodic symptoms consistent with mast cell mediator release affecting ≥2 organ systems; 2) a decrease in the frequency or severity, or resolution of symptoms with anti-mediator drug therapy; and 3) elevation of a validated urinary or serum marker of mast cell activation, such as the serum tryptase level (which is the marker of choice).[14-16]

In patients with mast cell activation symptoms, but with normal mast cell morphology/ immunophenotype without the *KIT* D816V mutation, other causes of mast cell activation should be considered (eg. secondary causes such as allergies, chronic inflammatory or neoplastic disorders, urticaria). In patients with mast cell activation symptoms for whom no cause is identified, a diagnosis of idiopathic MCAS is rendered on a provisional basis until a specific cause of mast cell activation is found.

More recently, some patients with MCAS and/or other systemic symptoms have been diagnosed with hereditary alpha-tryptasemia, a multi-system disorder characterized by duplications and triplications in the *TPSAB1* gene encoding a-tryptase. Elevation of the basal serum tryptase level is found in 4-6% of the general population. This condition is associated with elevation of the basal serum tryptase level as well as symptoms including cutaneous flushing and pruritus, dysautonomia, functional gastrointestinal symptoms, chronic pain, and connective tissue abnormalities, including joint hypermobility.[17] While it is currently unclear how this symptom complex relates to increased copy number of the *TPSAB1* gene, testing for this genetic variant may be considered.

Clinical Presentation

Mastocytosis is associated with a variety of symptoms related to the release of mast cell mediators.[18] While some patients present with isolated symptoms, others develop a constellation of symptoms related to mast cell activation. The most common clinical symptoms include flushing of the face, neck, and chest, pruritus, itching, hives, skin rashes, breathing difficulties (eg. wheezing and shortness of breath), rapid heart rate, chest pain, low blood pressure, dizziness, syncope, gastric distress (eg. diarrhea, nausea, vomiting, abdominal pain, bloating, gastroesophageal reflux disease), fatigue, musculoskeletal pain, and neuropsychiatric symptoms (eg. headache and/or brain fog, cognitive dysfunction, anxiety and depression).[19-22] Symptoms occur either spontaneously or in response to triggers of mast cell activation (eg. heat, cold or sudden temperature changes, physical and emotional stress, food, alcohol consumption, insect stings, venoms, infections, drugs [opioids, nonsteroidal anti-inflammatory drugs [NSAIDs], antibiotics and anesthetic agents], contrast dyes, surgery and other clinical procedures [eg. endoscopy, colonoscopy]).[19,22] Anaphylaxis can be a life-threatening manifestation of mast cell activation which requires immediate medical attention, the use of epinephrine, and other supportive care measures.

The mastocytosis quality-of-life questionnaire (MQLQ) and the mastocytosis symptom assessment form (MSAF) can be used for the assessment of symptoms at baseline and monitoring symptom status during the course of treatment in patients with ISM and SSM.[22]

In the WHO diagnostic criteria, clinical signs of disease related to SM are classified as B-findings or C-findings depending on the presence or absence of organ involvement and/or organ damage.[2] Evaluation of B-findings and C-findings is key to establishing the diagnosis of subtype of SM.

B-Findings

B-findings indicate a higher burden of SM and include: 1) high mast cell burden on bone marrow biopsy (>30% infiltration of cellularity by focal, dense aggregates of mast cells, AND serum tryptase level > 200 ng/ml); 2) hepatomegaly without impairment of liver function, palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging; and 3) signs of dysplasia or myeloproliferation in non-mast cell lineage(s), but criteria are not met for the definitive diagnosis of an associated hematological neoplasm (AHN), with normal or only slightly abnormal blood counts.

C-Findings

C-finding(s) are defined by one or more signs of organ damage due to infiltration by neoplastic mast cells, and are common in patients with advanced SM.[2] Examples of organ damage include cytopenia(s) (e.g. absolute neutrophil count < 1 x 10^9/L; hemoglobin < 10 g/dL, and/or platelet count < 100 x 10^9/L due to bone marrow dysfunction by neoplastic mast cell infiltration; palpable hepatomegaly with impairment

of liver function, ascites, and/or portal hypertension; skeletal involvement, with large osteolyses with or without pathologic fractures; palpable splenomegaly with hypersplenism; and malabsorption (e.g. hypoalbuminemia) with weight loss due of gastrointestinal mast cell infiltrates.[21]

Diagnostic Criteria For Variants Of Systemic Mastocytosis

Indolent Systemic Mastocytosis

ISM is characterized by low mast cell burden, no evidence of C-findings, or an AHN.[12] Patients exhibit a relatively younger age at presentation, lower incidence of constitutional symptoms (15%), and a higher prevalence of skin lesions (85%) and cutaneous symptoms (78%). Patients with ISM exhibit a life expectancy similar to that of an age-matched general population, with a median survival of 301 months.

Bone marrow mastocytosis (BMM) is a sub-variant of ISM in which mast cell infiltration is confined to the bone marrow with no skin or multiorgan visceral lesions.[12,23] The incidence of symptoms associated with mast cell mediator release is higher in BMM (86% compared to 67% for ISM and 50% for SSM) but the median survival is superior for patients with BMM (not reached compared to 301 months for ISM).[12]

Smoldering Systemic Mastocytosis

SSM is defined by ≥2 B-findings, and no evidence of C-findings or an AHN.[12] SSM is characterized by a relatively high mast cell burden, older age at presentation, and higher frequency of constitutional symptoms (45%). SSM is associated with inferior median survival (120 months compared to 301 months for ISM) and a significantly higher risk of transformation to acute myeloid leukemia (AML) or ASM (18% compared to <1% for ISM).[12] However, patients with SSM were significantly older and in a multivariate analysis, advanced age was the primary determinant of inferior overall survival (OS) and SSM was not independently associated with inferior OS. Owing to these clinical and prognostic differences (age distribution and risk of disease transformation), SSM was removed as a subcategory of ISM and listed as its own subvariant in the 2017 revised WHO classification.[2]

Aggressive Systemic Mastocytosis

The diagnosis of ASM requires the presence of one or more C-findings, but does not meet the criteria for mast cell leukemia (MCL).[2] The diagnosis of ASM indicates that only morphologic evidence for mast cell disease is found; conversely, the concomitant presence of an AHN indicates a diagnosis SM-AHN, even if C-findings are felt to be related to the mast cell component. Skin lesions are less common in ASM compared to ISM. The median survival of patients with ASM was 41 months in one study.[11]

Systemic Mastocytosis With An Associated Hematological Neoplasm

SM-AHN fulfills the diagnostic criteria for SM as well as the diagnostic criteria for the AHN.[2] SM-AHN is detected in about 40% of patients with SM. AHNs are of myeloid lineage in the overwhelming majority of patients and lymphoid neoplasms (e.g. chronic lymphocytic leukemia, lymphomas, multiple myeloma) are rarely observed. C-findings may or may not be present. AHNs include AML, myeloproliferative neoplasms (MPN), myelodysplastic syndromes (MDS), MDS/MPN (eg. chronic myelomonocytic leukemia (CMML) or MDS/MPN-unclassifiable (MDS/MPN-U), chronic eosinophilic leukemia, not otherwise specified (CEL, NOS).[11,24]

SM-AHN is characterized by older age at presentation, higher incidences of constitutional symptoms and hematological abnormalities

and an inferior OS compared with other subtypes of SM without AHN.[25] The outcome of patients with SM-AHN varies with the type of AHN. SM-MPN is associated with a significantly longer median survival (31 months; *P* = .003) compared to SM-CMML (15 months), SM-MDS (13 months), and SM-AML (11 months). The rate of leukemic transformation is more frequent in SM-MDS (29%) than in SM-MPN (11%) or SM-CMML (6%).[24]

Mast Cell Leukemia

MCL is defined histopathologically by the presence of ≥20% neoplastic mast cells on a bone marrow aspirate.[2] The aleukemic variant (<10% circulating mast cells in peripheral blood) is more common than the leukemic variant (≥10% circulating mast cells in peripheral blood). Acute MCL, characterized by the presence of C-findings/organ damage, is present in the majority of patients.[2] Chronic MCL is defined as MCL without C-findings/organ damage and may display a more indolent disease course over time, but its natural history requires more study.[26-28] Immunostaining with Ki-67 has been shown to differentiate between the acute and chronic variants, since most mast cells in chronic MCL stain negative for Ki-67 whereas mast cells in acute MCL frequently display Ki-67.[26] These findings require validation in additional studies.

MCL can either present as a *de novo* disorder or it can transform from advanced forms SM such as ASM or SM-AHN or very rarely, ISM.[11,29,30] MCL is associated with a poor prognosis regardless of the subtype or the presence of signs/symptoms of organ damage. In a study that evaluated the clinical and molecular characteristics of 28 patients with MCL, de novo MCL and secondary MCL resulting from leukemic transformation of SM-AHN or ASM were diagnosed in 57% and 43% of patients respectively, with no differences in clinical, morphological or molecular characteristics between the two variants.[30] AHNs (CMML, MDS/MPN unclassifiable, MDS and CEL) were diagnosed in 71% (20 out of 28) of patients. *KIT* D816V mutation was identified in 68% of patients and additional prognostically relevant mutations in *SRSF2, ASXL1* or *RUNX1* genes were identified in 52% of patients.

Workup

Evaluation for SM is recommended in patients with suspected clinical symptoms associated with the release of mast cell mediators or anaphylaxis, and/or increased serum tryptase level or adult onset mastocytosis of the skin (MIS).

Initial evaluation should include a history and physical exam, prior history of mast cell activation symptoms and potential triggers, skin exam for cutaneous lesions, palpation of spleen and liver, documentation of medications/transfusion history and weight loss. Laboratory evaluation should include comprehensive metabolic panel with uric acid, lactate dehydrogenase, and liver function tests, CBC with differential, and serum tryptase level. Peripheral blood smear should be reviewed for the presence of mast cells and/or for the evidence of other blood cell abnormalities (eg. eosinophilia, dysplasia, monocytosis).

Additional evaluations should include a bone marrow biopsy or biopsy of organ(s) with suspected extracutaneous involvement; high-sensitivity mutation analysis for the detection of *KIT* D816V mutation and myeloid mutation panel testing; mast cell immunophenotyping by immunohistochemistry (IHC) and/or flow cytometry; imaging studies to document organomegaly, lymphadenopathy, and/or ascites (e.g. B- and/or C-findings); and HLA testing, if considering allogeneic hematopoietic cell transplantation (HCT) as a future option. 24-hour urine studies to document biochemical evidence of mast cell activation

can be useful under selected circumstances. More details on the measurement of urinary metabolites are provided on MS-10.

Serum Tryptase Level

Serum tryptase is elevated in the vast majority of patients with SM across all subtypes.[31] Persistently elevated serum total tryptase (>20 ng/ml) is one of the minor criterion.[2] However, it is important to interpret elevated serum tryptase levels in the appropriate context since serum tryptase may also be transiently elevated during anaphylaxis or a severe allergic reaction.[32] Elevated levels of serum tryptase have also been documented in patients with other myeloid malignancies and hereditary alpha-tryptasemia[17,33,34] A minority of patients with SM have normal tryptase level possibly related to the lack of alpha tryptase genes described in Caucasian populations.[35]

Bone marrow evaluation should be done to confirm the diagnosis of SM in symptomatic patients with persistently elevated levels of serum tryptase.[34] While measurement of serum tryptase level is useful to estimate mast cell burden in patients with mastocytosis, such correlations may be confounded by the presence of an AHN which may also contribute to elevation of the serum tryptase level.[17,33,34]

Bone Marrow Evaluation

The detection of multifocal, dense infiltrates of mast cells (≥15 mast cells in aggregates) in the biopsy sections of the bone marrow and/or other extracutaneous organs is a major criterion for the diagnosis of SM. The presence of spindle-shaped or atypical mast cells in the trephine biopsy sections of bone marrow or bone marrow aspirate smears or other extracutaneous organs is one of the minor criteria.[2]

Bone marrow aspiration and biopsy with mast cell immunophenotyping is almost always necessary to establish the diagnosis of SM.[36] Bone marrow evaluation also helps in the detection of AHN, if present. Although bilateral bone marrow biopsies might be useful for the early diagnosis of SM or for the detection of minimal bone marrow involvement, a unilateral bone marrow biopsy is generally recommended.[37]

Mast Cell Immunophenotyping

Immunohistochemical evaluation is necessary to confirm the diagnosis of SM in patients with low mast cell burden or if bone marrow involvement is not morphologically conspicuous on the bone marrow aspirate or core biopsy by hematoxylin and eosin staining.[38,39] The expression of CD25, with or without CD2, in addition to normal mast cell markers, is a minor diagnostic criterion.[2]

Tryptase and CD117 are co-expressed on normal mast cells. Tryptase is considered the most sensitive marker since this allows for the detection of small and/or immature mast cell infiltrates. However, immunostaining with neither of these markers is able to distinguish between normal and neoplastic mast cells.[40-42] Aberrant expression of CD2 and CD25 has been reported to be useful to differentiate mast cells in SM from normal/reactive mast cells in the bone marrow.[42-44] Further studies have demonstrated that CD25 is a more sensitive marker than CD2, since the latter is not expressed in mast cells of advanced SM and is only expressed in about 50% to 60% of mast cells in cases of indolent SM.[41,45,46] The use of immunostaining for CD45 in combination with CD25 has been shown to specifically identify abnormal mast cells in patients with SM, a finding that has to be confirmed in further studies.[47]

Cytoplasmic and/or surface expression of CD30 has also been reported in neoplastic mast cells in patients with SM.[13,48-51] Earlier reports suggested that CD30 is preferentially expressed in the neoplastic mast

cells of advanced SM compared to ISM.[48,49] However, more recent reports confirm that CD30 is also frequently expressed in CM as well as in all subtypes of SM, suggesting that CD30 expression does not contribute to the differential diagnosis and prognostic stratification of different subtypes of SM.[50,51] However, increased expression of CD30 along with the absence of CD25 may be useful in the diagnosis of WDSM and its distinction from other subtypes of SM.[13]

IHC with markers for mast cell tryptase, CD117, and CD25 should be performed for the quantification of mast cell burden in bone marrow.[40-44] CD30 is considered optional; it can be useful in cases where CD25 is negative.[13] CD34 staining may also be obtained to quantify whether the proportion of myeloblasts are increased, especially in SM-AHN.[52] Flow cytometry is a complementary tool for the diagnosis or monitoring of SM. CD117, CD25, and CD2 are the standard markers; CD30 can also be considered.[53,54]

Molecular Testing

KIT D816V mutation occurs in the majority of patients (>90%) with SM.[6,24,55,56] In SM-AHN, the *KIT* D816V mutation can also be found in cells comprising the AHN. However, the frequency of *KIT* D816V mutation in these cells is variable depending on subtype of AHN, being most common in patients with SM-CMML (89%), and less frequent in patients with SM-MPN (20%) and SM-AML (30%).[57]

In addition to *KIT* D816V mutation, prognostically relevant mutations in several other genes (*TET2, SRSF2, CBL, ASXL1, RUNX1, JAK2,* and/or *RAS)* have also been identified in advanced SM (ASM, SM-AHN and MCL).[7,58-64] The presence of ≥1 mutations beyond *KIT* D816V has been associated with worse OS.[7] In addition, mutation(s) in *SRSF2*, *ASXL1* and/or *RUNX1* (S/A/R^{pos}) have been associated with significantly inferior OS.[61,62,64] A mutation-augmented prognostic scoring system (MAPSS) incorporating clinical and laboratory variables, as well as the *ASXL1* mutation has been developed to stratify patients with advanced SM into low-, intermediate- and high-risk with significantly different median survival (86 months, 21 months and 5 months respectively).[64] More refined prognostic scoring systems that include the results of S/A/R profiling are currently being developed. Myeloid mutation panel testing should be performed on the bone marrow, but can be performed on the peripheral blood in the presence of an AHN and/or circulating mast cells.

The *FIP1L1-PDGFRA* fusion oncogene resulting from the deletion of the CHIC2 locus at chromosome 4q12 usually presents as a chronic myeloid neoplasm with eosinophilia. Atypical or spindle-shaped mast cells that also express CD25 may be found in the bone marrows of such patients, usually in a loosely scattered or interstitial pattern without forming multifocal aggregates. While patients with the *FIP1L1-PDGFRA* fusion oncogene are not considered a subtype of SM, and *KIT* D816V is rarely found in these individuals, identifying the fusion in patients with eosinophilia is critical since it is a predictor of excellent response to imatinib.[65-67] The *FIP1L1-PDGFRA* fusion oncogene should be tested in patients with eosinophilia in peripheral blood who do not have the *KIT* D816V mutation.

KIT D816V Mutational Analysis

Detection of the *KIT* D816V mutation in the bone marrow, blood or another extracutaneous organ is included as a minor criterion.[2] Myeloid mutation panels are not recommended for the detection of *KIT* D816V since such next generation sequencing (NGS) assays exhibit low sensitivity.

Mutation analysis for *KIT* D816V is preferably done using the bone marrow sample since the yield from the peripheral blood may be lower. Several different sensitive assays have been used for the detection of *KIT* D816V mutation, including reverse transcriptase polymerase chain reaction (RT-PCR) plus restriction fragment length polymorphism (RFLP), nested RT-PCR followed by denaturing high-performance liquid chromatography (D-HPLC), peptide nucleic acid (PNA)-mediated PCR and allele-specific oligonucleotide quantitative reverse transcriptase polymerase chain reaction (ASO-qPCR).[68]

ASO-qPCR is a highly sensitive method for the detection of *KIT* D816V mutation in various tissues.[69] Recent studies have reported the possibility of detecting the *KIT* D816V in peripheral blood using a highly sensitive ASO-qPCR.[70-72] However, ASO-qPCR may not be useful for patients with low mast cell burden since *KIT* D816V mutation may not be detectable in the peripheral blood. In addition, ASO-qPCR also does not detect *KIT* mutations other than D816V (very rare occurring in <3% of patients). Therefore, if a diagnosis of SM is suspected, molecular testing with a highly sensitive ASO-qPCR assay can be first performed on peripheral blood in combination with measurement of the serum tryptase level and evaluation of clinical signs and/or symptoms suggestive of SM-related organ involvement. If positive, this should be followed by a detailed *KIT* mutation analysis on the bone marrow aspirate. *KIT* D816V mutational analysis on the bone marrow aspirate is particularly useful to establish the diagnosis of SM in patients with low mast cell burden, those with limited systemic disease who may have serum tryptase levels <20 ng/ml and lack multifocal mast cell clusters in a bone marrow biopsy.[38,39]

In patients with low mast cell burden who are otherwise negative for *KIT* D816V mutation, evaluation for *KIT* D816V mutation in the skin or an extracutaneous organ besides the bone marrow could be considered.[68]

In patients with a high mast cell burden who are otherwise negative for *KIT* D816V mutation, molecular testing should be confirmed with ASO-qPCR, if not originally obtained with this technique. If *KIT* D816V mutation is still negative, molecular testing for *KIT* mutations other than D816V should be done, preferably using PNA-mediated PCR.[73] Sequencing of the whole *KIT* by NGS may be undertaken.

Evaluation of B-Findings and C-Findings and Organ Involvement

B-findings and C-findings are used for the diagnosis of the WHO subtype of SM. The International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competency Network on Mastocytosis (IWG-MRT-ECNM) established eligible organ damage findings for enrollment of patients with advanced SM into clinical trials and to allow more stringent adjudication of organ damage responses to therapy. While WHO definitions of C-findings and IWG-MRT-ECNM-defined organ damage partially overlap, the latter criteria quantify the thresholds of SM-related organ damage that are eligible for response assessment on a clinical trial basis. This should permit harmonization of the types and severity of organ damage that are evaluable across studies of patients with advanced SM who are being treated with novel therapies (See Response Criteria).[2,74]

Imaging studies (CT/MRI or ultrasound of the abdomen/pelvis) are useful to document organomegaly, lymphadenopathy, and ascites in patients with advanced SM. Chest X-ray and/or CT of the thorax may be needed in selected circumstances to further assess whether pleural effusions are present in patients with advanced SM presenting with relevant pulmonary symptoms. C-findings (organ damage caused by mast cell infiltration) should be confirmed with appropriate organ-directed biopsy as needed with immunohistochemistry (e.g. CD117, CD25, tryptase).

Osteoporosis and osteopenia are the most common bone complications in patients with SM.[21] The risk of osteoporotic fracture is high in patients with ISM and higher urinary N-methylhistamine levels are also associated with a higher risk of osteoporosis.[75-77] Skeletal involvement, with large osteolytic lesions with or without pathological fractures is considered as a C-finding. However, the presence of one or more small lytic lesion(s) in the absence of other C-findings is insufficient to make a diagnosis of advanced SM and should not alone be considered an indication for cytoreductive therapy. Dual-energy x-ray absorptiometry (DEXA) scan to evaluate for osteopenia or osteoporosis and metastatic skeletal survey to evaluate for osteolytic lesions are recommended as part of the initial work up.

24-hour Urine Studies

The measurement of urinary metabolites of histamine and prostaglandin in a 24-hour urine sample has been shown to correlate with mast cell burden and activation.[78] N-methylhistamine, prostaglandin D2 and 2,3-dinor-11 beta-prostaglandin F2 alfa are the most commonly measured metabolites.[79-84] Any elevation above normal is considered significant; however; cut-off levels for significant elevation of these metabolites has not been established.

While 24-hour urine studies do not have much utility in patients with markedly elevated serum tryptase, the measurement of urinary metabolites may be useful in the diagnosis and initiation of appropriate targeted therapy for some of the mast cell activation symptoms (eg. higher urinary N-methylhistamine levels are associated with a higher risk of osteoporosis; certain symptoms associated with elevated urinary prostaglandin levels can be targeted with aspirin).[77,85]

Treatment Considerations

Referral to specialized centers with expertise in the management of mastocytosis is strongly recommended.[4,5] Multidisciplinary collaboration with sub-specialists (eg. anesthesia for invasive procedures/surgery; high-risk obstetrician for pregnancy) is recommended.

Patients should be counseled about the signs and symptoms of mast cell activation and the importance of avoiding known triggers of mast cell activation. The signs and symptoms of mast cell activation as well the potential triggers of mast cell activation are summarized in SM-H. Anaphylactic reactions are significantly more frequent in patients with ISM and should be managed with the use of epinephrine injection. All patients should carry 2 auto injectors of epinephrine to manage anaphylaxis. Pre-medications are recommended for most procedures in patients with SM, since surgery, endoscopy and other invasive and radiological procedures can induce mast cell activation and anaphylaxis.

Anti-mediator drug therapy for mast cell activation symptoms (as described below) is recommended for all patients with SM. Assessment of symptoms at baseline and monitoring symptom status during the course of treatment with MQLQ and MSAF is recommended for patients with ISM and SSM.[22] Patient-reported outcome instruments are currently under development for patients with advanced SM.

Cytoreductive therapy (discussed below) is recommended for patients with advanced SM (ASM, SM-AHN and MCL) owing to the frequent presence of organ damage and shortened survival of this patient population. In patients with SM-AHN, an initial assessment is undertaken to determine whether the SM component or the AHN component requires more immediate treatment. This determination can be challenging and reflects a comprehensive evaluation of several

factors, including the relative burden and/or stage of the SM and AHN disease components in the bone marrow and/or other extracutaneous organs. In some cases, organ-directed biopsy may be useful to determine whether organ damage is related to the SM or AHN or both (e.g. liver biopsy in a patient with liver function abnormalities). Although chronic MCL may follow a more indolent disease course compared to acute MCL with organ damage,[26-28] cytoreductive therapy should still be considered for such patients given the poor prognosis of both MCL subtypes.

Enrollment in well-designed clinical trials investigating novel therapeutic strategies (eg. selective KIT D816 inhibitors) is encouraged to enable further advances.

Anti-mediator Drug Therapy

Management of Chronic Symptoms Related To Mast Cell Mediator Release

A stepwise treatment approach for specific symptoms should be considered for all patients who present with symptoms related to mast cell mediator release, as outlined in SM-I. The treatment plan may vary according to specific patient scenarios. Standard doses need to be titrated. Higher doses may be necessary for symptoms refractory to standard dose treatment.

Histamine receptor type 1 (H1) and histamine receptor type 2 (H2) blockers have been shown to control skin symptoms (eg. pruritus, flushing, urticaria, angioedema dermatographism), gastrointestinal symptoms (eg. diarrhea, abdominal cramping, nausea and vomiting), neurological (eg. headache, poor concentration and memory, brain fog), cardiovascular (eg. pre-syncope, syncope, tachycardia, pulmonary (eg. wheezing, throat swelling) and naso-ocular symptoms (nasal stuffiness or pruritus, conjunctival injection).[86]

Cromolyn sodium is effective for the management of cutaneous, gastrointestinal and neurological symptoms.[87,88] In one double blind cross over study, cromolyn sodium resulted in marked amelioration of skin pruritus, whealing, flushing, diarrhea, abdominal pain, as well as disorders of cognitive function compared to placebo.[87] In another double blind, cross-over study, while cromolyn sodium was significantly beneficial for the treatment of gastrointestinal symptoms (diarrhea, abdominal pain, nausea, and vomiting) compared to placebo, the benefit for nongastrointestinal symptoms was not statistically significant.[88] Cromolyn sodium in the form of ointment or cream can be used to decrease flare ups of cutaneous symptoms in response to triggers.

Aspirin, corticosteroids and leukotriene receptor antagonists are useful for the management of symptoms that are refractory to other treatment options.[86] In particular, leukotriene receptor antagonists have been used for the management of skin and gastrointestinal symptoms that have not responded to other therapies.[89,90] Aspirin has been shown to be effective for the management of symptoms associated with elevated urinary prostaglandin levels.[91] However, the risks and benefits of aspirin need to be weighed carefully since it can trigger mast cell activation in some patients.

Omalizumab, anti-immunoglobulin E (IgE) monoclonal antibody, can be used for the management of mast cell activation symptoms, insufficiently controlled by conventional therapy.[92] Omalizumab was particularly effective for recurrent anaphylaxis and skin symptoms than for gastrointestinal, musculoskeletal, and neuropsychiatric symptoms.[92]

Management of Anaphylaxis

The prevalence of anaphylaxis has been reported in 24% to 49% of patients with SM.[19,93,94] Increased serum tryptase levels has been

identified as a risk factor for anaphylaxis in some studies[19,95] whereas other studies have identified absence of mastocytosis in skin, atopic SM, low baseline tryptase levels and higher total IgE levels as risk factors for severe anaphylaxis.[95-97]

Hymenoptera venom allergy is an IgE-mediated hypersensitivity to the allergens in insect venom and accounts for 2% to 34% of all cases of anaphylaxis.[98,99] Hymenoptera venom allergy remains the only established risk factor for severe recurrent anaphylaxis in patients with SM.[100] Hymenoptera venom anaphylaxis is more prevalent in patients with ISM and it seems to be absent in patients with the advanced SM with high mast cell burden.[101] Hymenoptera anaphylaxis may be the presenting symptom of mastocytosis in an otherwise healthy individual. Therefore, mastocytosis should be suspected in patients who present with anaphylactic reactions after Hymenoptera sting.

Elevated baseline serum tryptase levels and mastocytosis are considered risk factors for severe Hymenoptera venom anaphylaxis.[102-105] In addition, vespid venom allergy, older age, male sex, angiotensin-converting enzyme (ACE) inhibitor therapy, and previous insect stings with a less severe systemic reaction have also been identified as predictors of systemic anaphylactic reactions in patients with Hymenoptera venom allergy.[104] *KIT* D816V mutation has been implicated in the hyperactivity of mast cells by amplifying the IgE-dependent mast cell mediator release.[106] However, the exact mechanism of increased susceptibility to Hymenoptera venom anaphylaxis has not been elucidated in patients with SM.

Anaphylactic symptoms should be treated with epinephrine as first line therapy. Antihistamines (H1 and H2 blockers) and steroids can be added as required. Systemic hives with no organ involvement can be managed with the use of antihistamines. Epinephrine injection is the preferred treatment for systemic hives with organ involvement (upper/lower airway, gastrointestinal, neurological, cardiovascular) or an acute onset of anaphylaxis with the following symptoms: hypotension, laryngeal edema, vasomotor collapse, oxygen desaturation, and/or seizures.[99]

Venom immunotherapy (VIT) is effective for the treatment of IgE-mediated Hymenoptera venom anaphylaxis in patients with SM and it has also been to significantly reduce the risk of anaphylaxis after a re-sting.[107-110] VIT is recommended for all patients with a positive skin test or a positive test for Hymenoptera specific IgE antibodies as well as for those with a history of Hymenoptera venom anaphylaxis after an insect sting.[99]

Omalizumab is an effective treatment option for unprovoked anaphylaxis, Hymenoptera venom- or food-induced anaphylaxis in patients with a negative skin test or those with a negative test for specific IgE antibodies.[111,112] Omalizumab also can improve tolerance while on VIT.

Management of Osteoporosis

The use of bisphosphonates (with continued use of antihistamines) is recommended to resolve bone pain and improve vertebral bone mineral density (BMD).[113] Pamidronate and zoledronic acid have demonstrated efficacy, resulting in significant increases in spine and hip BMD and decreases of bone turnover markers in a small series of patients with SM.[114,115] Interferon-alfa or pegylated interferon alfa may be considered for patients with refractory bone pain and/or worsening bone mineral density on bisphosphonate therapy.[116-118]

Denosumab, an anti-RANKL monoclonal antibody, has also been associated with significant increases in BMD at lumbar and femoral

sites, decreases in bone turnover markers in serum (mainly C-terminal telopeptide of collagen type I and bone alkaline phosphatase to a lesser extent).[119] Denosumab can be used as an alternative treatment option for patients with bone pain not responding to bisphosphonates or for patients who are not candidates for bisphosphonates because of renal insufficiency. Vertebroplasty or kyphoplasty could also be used in selected patients for refractory pain associated with vertebral compression fractures.[120]

Cytoreductive Therapy

Midostaurin

Midostaurin, an oral multikinase inhibitor, has demonstrated activity for the treatment of advanced SM (ASM, SM-AHN and MCL).[121-123] In an open-label study of 116 patients with advanced SM, 89 patients had evaluable mastocytosis-related organ damage: 16 patients with ASM, 57 patients with SM-AHN, and 16 patients with MCL. Treatment with midostaurin (100 mg twice daily) resulted in an overall response rate (ORR) of 60% (45% of the patients had a major response, defined as complete resolution of at least one type of mastocytosis-related organ damage).[121] Response rates were similar across all subtypes of advanced SM, *KIT* mutation status (63% for patients who were *KIT* D816V mutation-positive and 44% for those who were *KIT* D816V mutation-negative or unknown mutation status) or exposure to previous therapy. The median OS and progression-free survival (PFS) were 29 months and 14 months respectively. The median OS and PFS were longer for patients with ASM (not reached and 29 months, respectively) than for patients with SM-AHN (21 months and 11 months, respectively) and MCL (9 months and 11 months, respectively). In a multivariate analysis, a subtype of advanced SM other than MCL and ≥50% reduction of bone marrow mast cell burden were identified as independent predictors of longer OS. Low-grade nausea, vomiting, and diarrhea were the most frequent adverse events. New or worsening grade 3 or 4 neutropenia, anemia, and thrombocytopenia occurred in 24%, 41%, and 29% of the patients respectively, and were more common in patients with pre-existing cytopenias. Midostaurin was approved by the Food and Drug Administration (FDA) in 2017 for patients with a diagnosis of ASM, SM-AHN, or MCL.

A recent study that evaluated the impact of *KIT* D816V mutation and other molecular markers on the clinical outcome of 38 patients with advanced SM treated with midostaurin found that the ORR, median duration of midostaurin treatment, and overall survival (OS) were significantly higher in patients with a S/A/R^{neg} (vs S/A/R^{pos}) mutation profile and in patients with a ≥25% (vs. <25%) reduction in the *KIT* D816V allele burden using ASO-qPCR. The acquisition of additional mutations in *KRAS, NRAS*, *RUNX1*, *IDH2*, or *NPM1* genes was identified in patients with disease progression.[124]

Cladribine

Cladribine (2-chlorodexyadnosine) is not approved by the FDA for SM, but is used on an off-label basis because of its activity across a spectrum of SM subtypes, including MCL refractory to prior cytoreductive therapy.[125-127] In an analysis 108 patients with SM treated with cytoreductive therapy, cladribine resulted in an ORR of 56%, 50%, 55% respectively, in patients with ISM, ASM and SM-AHN.[126] The presence of circulating immature myeloid cells was a predictor of inferior response. In a more recent study that reported the long-term safety and efficacy of cladribine in 68 patients with SM, the ORR was 72%, split between 92% for patients with ISM (major/partial 56%/36%) and 50% for those with advanced SM (major/partial 38%/13%). The median duration of response was 4 years and 3 years for ISM and ASM, respectively.[127] In a multivariate analysis, only mastocytosis subtypes (SM-AHN vs. ISM; *P* =.02 and ASM vs ISM; *P* = .006) and age

> 50 years at diagnosis were independently associated with mortality. Lymphopenia (82%), neutropenia (47%), and opportunistic infections (13%) were the most frequent grade 3 or 4 toxicities. Because of its toxicity profile, for patients with advanced SM, cladribine may be particularly useful when rapid debulking of disease is required. However, cladribine may also be useful in selected patients with ISM or SSM with severe, refractory symptoms related to mast cell mediator release or bone disease not responsive to anti-mediator drug therapy or bisphosphonates.

Interferons

Standard and pegylated formulations of interferon alfa (with or without prednisone) also elicit responses across all subtypes of SM, but because of its cytostatic mechanism of action, responses may take longer to emerge, and may be more suitable for patients with slowly progressive disease without the need for rapid cytoreduction. Interferon alfa can induce marked reduction in serum and urine metabolites of mast cell activation, reduce symptoms related to mast cell mediator release, resolve cutaneous lesions, improve skeletal disease, and improve both bone marrow mast cell burden and C-findings.[126,128-131] In a retrospective study evaluating the efficacy of different cytoreductive therapies in SM, the ORR was 47% and 57%, respectively, among patients treated with interferon alfa with or without prednisone.[126] The ORR in patients with ISM, ASM and SM-AHN were 60%, 60% and 45% respectively. Absence of systemic mediator-related symptoms was significantly associated with inferior response rates. Fatigue, depression and thrombocytopenia were the most common toxicities.

Imatinib

Imatinib is approved by the FDA for the treatment of adult patients with ASM without the *KIT* D816V mutation (including wild-type) or with unknown mutational status. For example, it has shown activity against the *KIT* F522C transmembrane mutation, V560G juxtamembrane mutation, germline K509I mutation, deletion of codon 419 in exon 8, and p.A502_Y503dup mutation in exon 9.[132-139] As previously noted, imatinib is very effective in the treatment of patients with eosinophilia-associated myeloid neoplasms characterized by the *FIP1L1-PDGFRA* fusion tyrosine kinase.[65] In a study that evaluated the efficacy of imatinib in 10 patients with SM lacking the *KIT* D816V mutation and meeting criteria for WDSM (including 3 patients with ISM and 3 patients with MCL), imatinib resulted in an ORR of 50%, including early and sustained complete response in 4 patients and partial response in one patient with wild-type *KIT*.[139]

Allogeneic HCT

Allogeneic HCT has been evaluated in patients with advanced SM and the outcomes are significantly affected by the subtype of SM and the type of conditioning regimen used.[140-142] In the largest retrospective analysis that included 57 patients with advanced SM (median age, 46 years; SM-AHN, n = 38; MCL, n = 12; ASM; n = 7), allogeneic HCT was associated with 70% response rate (28% CR; 21% SD) and the 3-year OS rate was 57% for all patients (74% for patients with SM-AHN; 43% and 17% respectively, for patients with ASM and MCL).[142] MCL subtype was the strongest risk factor for poor OS. Reduced intensity conditioning regimens were associated with lower survival than myeloablative conditioning regimens. The role of allogeneic HCT needs to be determined in a prospective trial. However, given the rarity of SM, no larger prospective trials of HCT have been initiated to confirm the role of allogeneic HCT.

In 2016, a consensus opinion was published on indication for allogeneic HCT in patients with advanced SM.[143] Allogeneic HCT can be considered as an initial treatment option for patients with ASM and

acute MCL. Among patients with SM-AHN, allogeneic HCT should be considered as part of initial treatment when the AHN component requires HCT and it should also be considered if the SM component presents as advanced SM or progresses to advanced SM during treatment. Prophylactic anti-mediator drug therapy (corticosteroids, anti-histamines and epinephrine) should be used with the conditioning regimen in all patients.[143]

Response Criteria

Response criteria for advanced SM were first published in 2003 and were subsequently modified in 2013 by the IWG-MRT and ECNM with the addition of more specific and quantifiable criteria to establish eligible organ damage findings for clinical trial enrollment and facilitate response evaluation to targeted therapies.[74,144] These response criteria were developed mainly for use in clinical trials. In addition to the IWG-MRT-ECNM response criteria, treatment response criteria have also been published to adjudicate responses in the AHN component.

The revised 2013 IWG-MRT-ECNM response criteria delineate definitions for nonhematologic and hematologic organ damage eligible for response evaluation and adjudication of response.[74] Absolute neutrophil count (ANC), transfusion-dependent and independent anemia and thrombocytopenia are used for the assessment of hematologic organ damage. Nonhematologic organ damage is assessed based on the presence of symptomatic ascites or pleural effusion, liver function abnormalities, hypoalbuminemia and symptomatic marked splenomegaly. The development of ascites usually reflects aggressive liver disease and may be accompanied by hepatomegaly, abnormal liver function test results and/or portal hypertension. Hypoalbuminemia is indicative of worsening synthetic function of the liver and/or worsening nutritional status due to gastrointestinal tract infiltration by neoplastic mast cells.

Clinical improvement (CI) is defined as the resolution of ≥1 findings of nonhematologic or hematologic organ damage without concomitant worsening of other eligible organ damage.[74] Complete response (CR) and partial response (PR) are defined based on the percent reduction in bone marrow mast cells and the reduction of serum tryptase levels.[74] In addition, the achievement of a CR or PR also requires the resolution of all or at least one CI findings, respectively. Responses (resolution of findings of organ damage as well as reduction in bone marrow mast cell burden and serum tryptase level) should be maintained or confirmed for a period of at least 12 weeks in order to fulfill the criteria for CI, CR and PR. Additional criteria are also included for progressive disease (PD), stable disease (SD), and loss of response. The response criteria are summarized in SM-F.

Monitoring Response and Additional Therapy

ISM or SSM

History and physical exam, laboratory evaluation (annually for patients with ISM and every 6-12 months for patients SSM), DEXA scan (every 1-3 years for patients with osteopenia or osteoporosis) and assessment of symptom burden and QOL using MSAF and MQLQ is recommended for patients with ISM and SSM.

Although increased serum beta-2-microglobulin has been identified in one study as an independent predictor of disease progression in patients with ISM, this is not routinely performed in clinical practice.[10] Progressively increasing serum tryptase levels has been associated with disease progression to SSM or ASM and shorter PFS in patients with ISM.[145] Patients with ISM and SSM should also be monitored for

the development of signs of disease progression to advanced SM (eg. development of B-findings and/or C-findings/organ damage).

Advanced SM

Bone marrow aspirate and biopsy with cytogenetics, serum tryptase level and additional staging studies to document organ damage are recommended for patients with ASM, SM with AHN and MCL, if supported by increased symptoms and signs of progression (return or progression of hematologic or nonhematologic organ damage; symptomatic or progressive hepatomegaly or splenomegaly).[74] Repeat NGS panel testing may be considered to determine whether signs of disease progression are associated with the development of new mutations compared to baseline.

Biopsy of involved extramedullary organ may be considered to evaluate the grade and extent of SM-related organ damage.[74] Evaluation of organ damage in SM with an AHN might require a tissue biopsy to ascertain the relationship between organ damage and burden of mast cell infiltration and/or AHN involvement.[74] Additional staging studies include complete blood count for the evaluation of hematologic organ damage, liver functions tests (measurement of total bilirubin, alanine aminotransferase, aspartate aminotransferase, and serum alkaline phosphatase [the most common SM-associated sign of hepatic damage]) for the evaluation of nonhematologic organ damage and imaging studies (CT or MRI) to verify physical examinations findings of organ involvement or organ damage.

KIT D816V allele burden has been shown to correlate with serum tryptase levels and response to cytoreductive therapy. However, the role of *KIT D816V* allele burden in monitoring response is not yet well established.[146,147]

Additional Therapy

The panel acknowledges that the 2013 IWG-MRT-ECNM response criteria were developed mainly for use in clinical trials and that clinical benefit may not reach the threshold of these response criteria.[74] Response assessment should be based on the improvement of mast cell activation symptoms and SM-related organ damage at the discretion of the clinician.

Continuation of prior treatment is recommended for patients achieving adequate response to anti-mediator drug therapy (ISM or SSM) or cytoreductive therapy (advanced CM). Evaluation of allogeneic HCT should be considered for patients with advanced SM (ASM, SM-AHN or MCL) with adequate response to cytoreductive therapy and with suitable donor(s) identified.[142,143]

Patients with ISM or SSM with inadequate response or loss of response or progression to advanced SM should be managed with cytoreductive therapy. Patients with advanced SM with inadequate response or loss of response should be treated with alternate cytoreductive therapy not previously received. Restaging studies (as described above) are recommended prior to initiation of additional therapy.

Special Considerations

Surgery

Mast cell activation can occur in patients with mastocytosis undergoing surgical procedures and the risk may persist for several hours after surgery due to delayed mast cell mediator release.[148] The primary goal is to prevent mast cell activation during and in the immediate aftermath of the surgical procedure. Multidisciplinary management is recommended with the involvement of surgical, anesthesia and perioperative medical teams. Careful review of prior anesthetic records

as well as identification and avoidance of known triggers for mast cell activation symptoms (such as temperature extremes [hypothermia or hyperthermia] and unnecessary trauma) is strongly recommended.[149]

The efficacy and safety of perioperative drugs in patients with SM has not been fully established, although anecdotal reports suggest that certain perioperative drugs are considered safer in patients with SM.[150] Nevertheless, the use of perioperative drugs is not contraindicated in patients with SM.[149,151] While it is important that analgesics should not be withheld from patients with SM (since pain can be a trigger for mast cell activation), caution should be exercised with the use of opioids (eg, codeine or morphine).

Management of mast cell activation symptoms depends on their severity of symptoms. The use of benzodiazepines, anti-histamines (H1 and H2 blockers) and corticosteroids, is probably helpful in reducing the frequency and/or severity of mast cell activation symptoms.[149,150] Other options include fluid resuscitation, intravenous epinephrine and discontinuation of the suspected drug or anesthetic agent.[149] The risk of anaphylaxis in the perioperative period is estimated to be higher patients with SM relative to the general population.[151] In the event of anaphylaxis or other mast cell activation event, a full allergic workup should be initiated.[151,152] The workup should include skin tests or detection of specific IgE antibodies for the identification of IgE-mediated hypersensitivity to drugs and measurement of serum tryptase level within 30–120 minutes of onset of symptoms and also after full recovery.[149,150]

Pregnancy

Although mast cells have been associated with beneficial effects in early stages of pregnancy (in terms of implantation, placentation and fetal growth), in later stages of pregnancy, excessive release of mast cell mediators is associated with pre-term delivery.[153] The diagnosis of SM does not appear to have any effect on fertility. There is limited evidence regarding the impact of mastocytosis on pregnancy compared to the general population. Spontaneous miscarriages and worsening of symptoms related to mast cell activation have been reported in 20% to 30% of pregnant women with mastocytosis.[154-156] Symptoms related to mast cell mediator release have been observed in 11% of patients without any fatal outcome.[156]

SM is not a contraindication to a successful pregnancy. Pregnant women with SM should be managed by a multidisciplinary team, including a high-risk obstetrician and anesthesiologist during the pre-conception, pregnancy, and the peripartum period. Management of SM during pregnancy involves alleviation of symptoms related to mast cell activation with the use of acceptable medications to minimize potential harm to the fetus. Breast-feeding by patients with SM should be done in consultation with a pediatrician and International Board Certified Lactation Consultant (IBCLC).

Avoidance of known triggers and prophylactic anti-mediator drug therapy (corticosteroids, anti-histamines and epinephrine) are standard approaches during pregnancy and early post-partum period.[157,158] Cytoreductive therapy with interferon-alfa can be considered for pregnant women with severe symptoms that are refractory to conventional therapy. However, the use of cladribine, imatinib and midostaurin is not recommended. Medications used to treat SM and their potential risks during both pregnancy and lactation are summarized in SM-J.

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