National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Systemic Mastocytosis

Version 3.2024 — April 24, 2024

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National Comprehensive Cancer Network®

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Systemic Mastocytosis

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Discussion

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.

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

– Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 3.2024 of the NCCN Guidelines for Systemic Mastocytosis from Version 2.2024 include:

MS-1
• The discussion has been updated to reflect the changes in the algorithm.

Updates in Version 2.2024 of the NCCN Guidelines for Systemic Mastocytosis from Version 1.2024 include:

SM-K 4 of 4
Treatment for Osteopenia/Osteoporosis
• Added footnote g: An FDA-approved biosimilar is an appropriate substitute.

Updates in Version 1.2024 of the NCCN Guidelines for Systemic Mastocytosis from Version 4.2023 include:

SM-2
• Classification, modified Treatment for mast cell leukemia to include ± *AHN* (Also for SM-4).

SM-4
• Column 3, modified to include: Useful in certain circumstances: Cladribine or Peginterferon alfa-2a.

Footnotes
• o, modified 2nd sentence: ...useful in *certain circumstances for* select~~ed~~ patients....
• s, deleted 2nd sentence: For the management of avapritinib toxicity, see SM-L (Also for SM-5, SM-7, SM-8).
• t, new: Refer to the package insert for the full prescribing information, dose modifications, and monitoring for adverse reactions: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. (Also for SM-5, SM-7,SM-8).
• u, new reference: Gotlib J, et al. NEJM Evid 2023;2:EVIDoa2200339.

SM-5
• Column 1, modified: ...*ICC* criteria or eligible organ damage findings per ~~IWG-MRT-ECNM~~ *clinical trial response* criteria.
• Column 5, modified: Re-stage, consider second-line therapy and Consider allogeneic HCT (Also for SM-7, SM-8).

Footnotes
• Deleted: For the management of midostaurin toxicity, see SM-M. (Also for SM-7, SM-8).
• x, modified: Clinical benefit may not reach the threshold of the ~~2013 IWG-MRT-ECNM~~ *clinical trial* response criteria. (Also for SM-7, SM-8).

SM-6
• Column 3, top pathway, modified: Does AHN component require ~~more immediate treatment~~ *prioritization over SM component*?
  ▸ bottom pathway, modified: Does SM component require *prioritization over AHN component* ~~more immediate treatment~~ (eg, 1 or more C-findings)?

SM-7
• Column 1,modified: SM-AHN SM component requiring *prioritization over AHN component* ~~more immediate treatment~~ (eg, 1 or more C-findings)
• Column 3, middle pathway, modified: Progression of AHN, ~~requiring treatment~~

SM-8
• Modified page title to include: ± Associated Hematologic Neoplasm.

SM-A
• Added footnote: See discussion for WDSM.

SM-E
• Modified page title: Criteria for B-Findings ~~and C-Findings~~ in Patients with Systemic Mastocytosis.
• Deleted: Burden of Disease (B-Findings)
• Added to footnote a: *The diagnosis of BMM requires no B- or C-findings;* deleted: or MCL (MCs ≥20% on bone marrow smears) (Also for SM-F)

SM-F
• Modified page title: Criteria for ~~B-Findings and~~ C-Findings in Patients with Systemic Mastocytosis.
• Deleted: Burden of Disease (C-Findings)

SM-J
• Musculoskeletal, modified: to include ...osteopenia, osteoporosis, *focal bone pain concerning for fractures*

SM-K, 1 of 4
• Added footnote: *First-generation anticholinergic antihistamines are not recommended in adult patients >65 years of age.* Also for SM-L 1 of 4.

SM-L, 2 of 4
• Bullet 6, 3rd sentence, deleted: (risk category C).

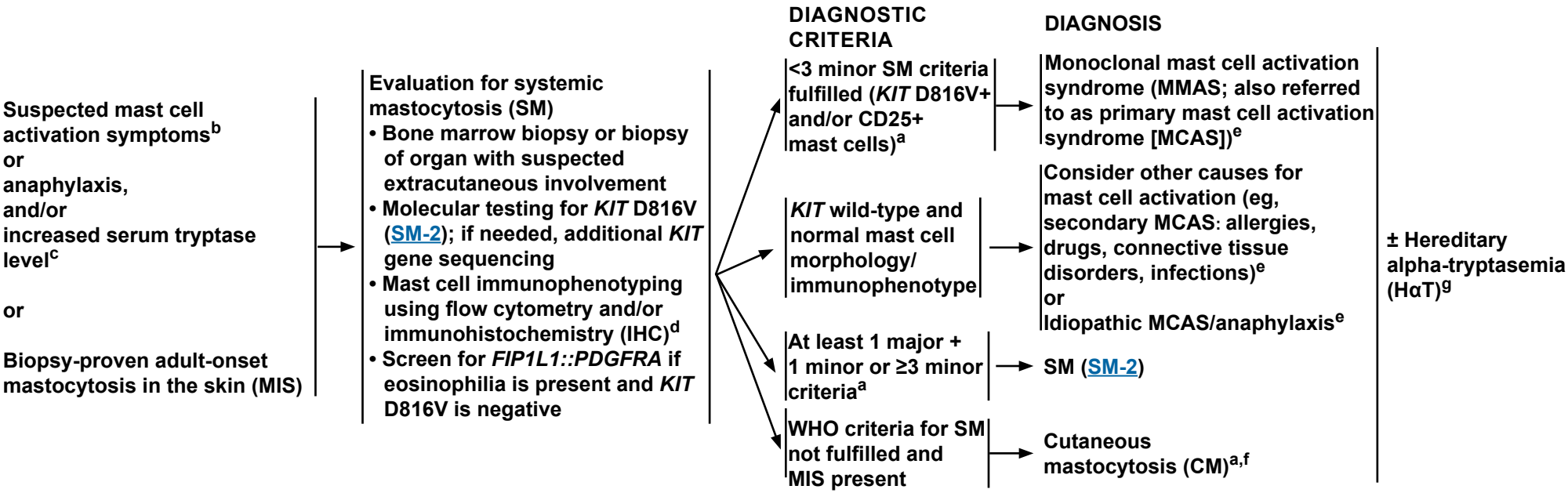
SM-L, 3 of 4
• Removed: Risk category and category descriptions. (Also for SM-L 4 of 4).

SM-L, 4 of 4
• Pregnancy implications, for imatinib, removed: Pregnancy not recommended within 2 wk of last imatinib dose ~~(in patient with reproductive potential)~~.

SM-M and SM-N
• Removed the pages for Management of Avapritinib and Midostaurin Toxicity.

Continued

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



[a] The diagnosis of mastocytosis and its subtypes requires a combination of histopathologic, clinical, laboratory, and cytogenetic/molecular analyses. See 2022 Classification of Mastocytosis (SM-A); WHO Diagnostic Criteria for Cutaneous Mastocytosis (SM-B); 2022 Diagnostic Criteria for Systemic Mastocytosis (SM-C); and Diagnostic Criteria for the Variants of Systemic Mastocytosis (SM-D).

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

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

[d] Mast cell markers by flow cytometry immunophenotyping include CD117, CD25, CD30, and CD2. IHC markers include CD117, CD25, CD30, and tryptase. Also see SM-2.

[e] Specific criteria have been established for primary and secondary MCAS (Akin C. J Allergy Clin Immunol 2017;140:349-355). See Discussion.

[f] Management of CM is not included in these guidelines. Referral to centers with expertise in CM is strongly recommended.

[g] HαT is a multisystem 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, et al. Nat Genet 2016;48:1564-1569). HαT may be diagnosed alone, but is also enriched in patients with SM, especially indolent or smoldering SM (ISM/SSM). It may also be found in patients with CM. HαT is associated with an increased risk of severe mediator symptoms/anaphylaxis. (Greiner G, et al. Blood 2021;137:238-247 and Lyons JJ, et al. J Allergy Clin Immunol 2021;147:622-632).

Adapted from: Pardanani A. Systemic mastocytosis in adults: 2021 update on diagnosis, risk stratification and management. Am J Hematol 2021;96:508-525.

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WORKUP FOR SUSPECTED SYSTEMIC MASTOCYTOSIS[h]

General Diagnostic Studies

- H&P, including prior history of mast cell activation symptoms; history of anaphylaxis; potential triggers; examination for MIS; spleen and liver size by palpation; and 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
- Complete blood count (CBC) with differential
- Examination of blood smear (eg, monocytosis, eosinophilia, dysplasia)[i]
- Bone marrow aspirate and biopsy with[i]:
  - Flow cytometry: CD34, CD117, CD25, CD30, CD2
  - IHC: CD117, CD25, CD30, tryptase
  - Cytogenetics
- Fluorescence in situ hybridization (FISH) as needed for associated hematologic neoplasm (AHN)-related abnormalities[i]
- Molecular testing for *KIT* D816V using an assay with high sensitivity (eg, allele-specific oligonucleotide quantitative reverse transcriptase polymerase chain reaction [ASO-qPCR] or digital droplet polymerase chain reaction [PCR]).[i,j,k] If negative for *KIT* D816V mutation and eosinophilia is present, then screen for *FIP1L1::PDGFRA* gene fusion.
- Multigene next-generation sequencing (NGS) panel that includes genes such as *SRSF2, ASXL1,* and *RUNX1*[i,j,k]

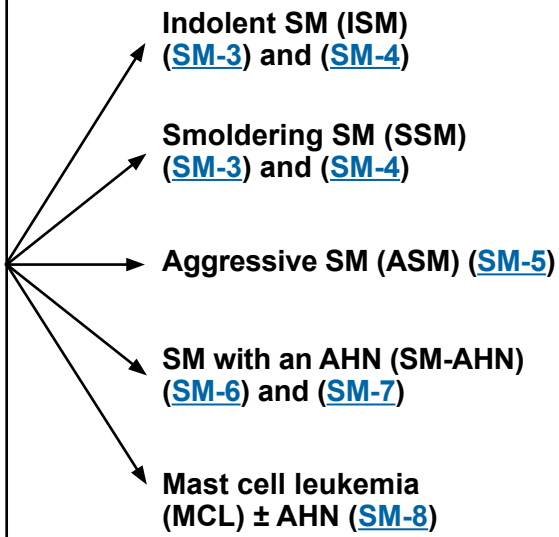
Evaluation of B- and C-Findings and Organ Involvement[l]

- CT/MRI or ultrasound of the abdomen/pelvis
- Dual x-ray absorptiometry (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 IHC (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
- Human leukocyte antigen (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[h]



[h] Diagnostic criteria for the variants of Systemic Mastocytosis (SM-D).
[i] Recommendations for Histopathology Analysis and *KIT* D816V Mutation Testing in Systemic Mastocytosis (SM-H).
[j] Preferred on the bone marrow, as yield from the peripheral blood may be lower; exceptions may be patients with SM-AHN or MCL. See SM-H 2 of 3.
[k] Adverse prognostic variables and risk stratification in Systemic Mastocytosis (SM-I).
[l] IWG-MRT-ECNM and modified IWG-MRT-ECNM criteria are used to establish eligible organ damage findings for clinical trial enrollment and to adjudicate response to therapy. The proposed ECNM-AIM response criteria use the same organ damage to assess response (SM-G). B- and C-findings are used for the diagnosis of the WHO subtype of SM (SM-D, SM-F).
[m] van Anrooij D, 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."

Note: All recommendations are category 2A unless otherwise indicated.
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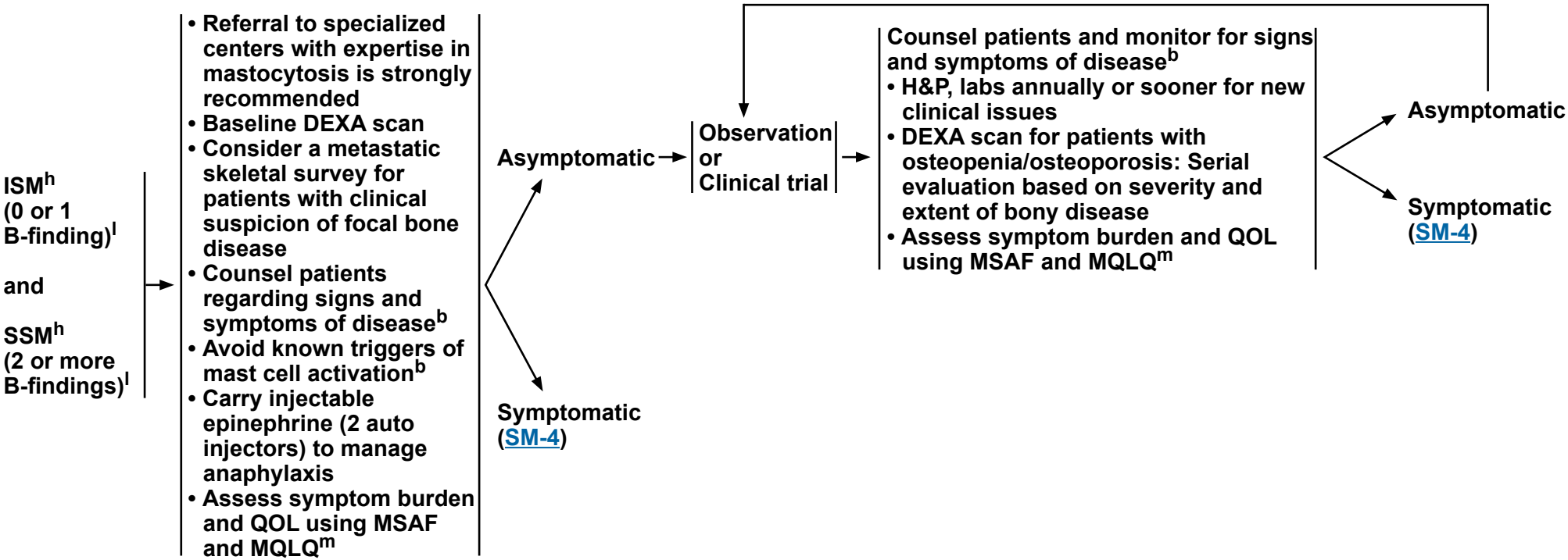
TREATMENT FOR INDOLENT SYSTEMIC MASTOCYTOSIS AND SMOLDERING SYSTEMIC MASTOCYTOSIS[k]



[b] Patients should be counseled about the signs/symptoms and potential triggers of mast cell activation (SM-J). Multidisciplinary collaboration with sub-specialists (eg, anesthesia for procedures/surgery; high-risk obstetrics for pregnancy) is recommended (SM-L).
[h] Diagnostic criteria for the variants of Systemic Mastocytosis (SM-D).
[k] Adverse prognostic variables and risk stratification in Systemic Mastocytosis (SM-I).
[l] IWG-MRT-ECNM and modified IWG-MRT-ECNM criteria are used to establish eligible organ damage findings for clinical trial enrollment and to adjudicate response to therapy. The proposed ECNM-AIM response criteria use the same organ damage to assess response (SM-G). B- and C-findings are used for the diagnosis of the WHO subtype of SM (SM-D, SM-E, SM-F).
[m] van Anrooij D, 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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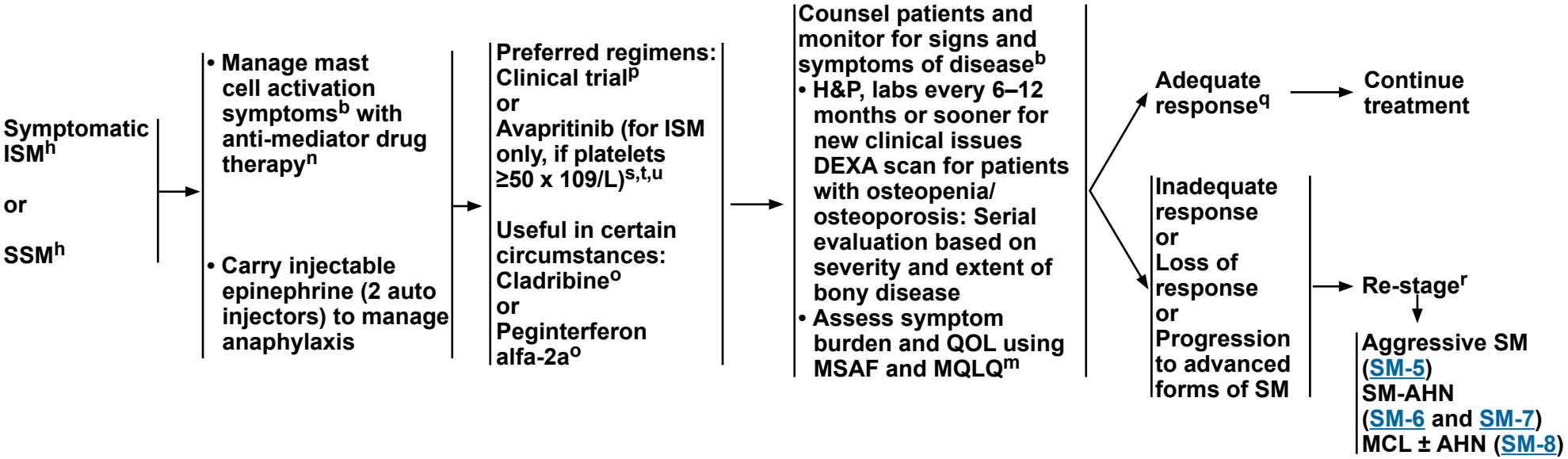

[b] Patients should be counseled about the signs/symptoms and potential triggers of mast cell activation (SM-J). Multidisciplinary collaboration with sub-specialists (eg, anesthesia for procedures/surgery; high-risk obstetrics for pregnancy) is recommended (SM-L).

[h] Diagnostic criteria for the variants of Systemic Mastocytosis (SM-D).

[k] Adverse prognostic variables and risk stratification in Systemic Mastocytosis (SM-I).

[m] van Anrooij D, 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."

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

[o] Cladribine and peginterferon alfa-2a are generally recommended only for patients with advanced SM. However, these agents may also be useful in certain circumstances for select patients with ISM or SSM with severe, refractory mediator symptoms or bone disease not responsive to anti-mediator therapy or bisphosphonates.

[p] Ongoing trials are underway. See Discussion for further details.

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

[r] 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.

[s] Avapritinib is not recommended for the treatment of patients with platelet counts of less than 50 X 10^9/L.

[t] Refer to the package insert for the full prescribing information, dose modifications, and monitoring for adverse reactions: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

[u] Gotlib J, et al. NEJM Evid 2023;2:EVIDoa2200339.

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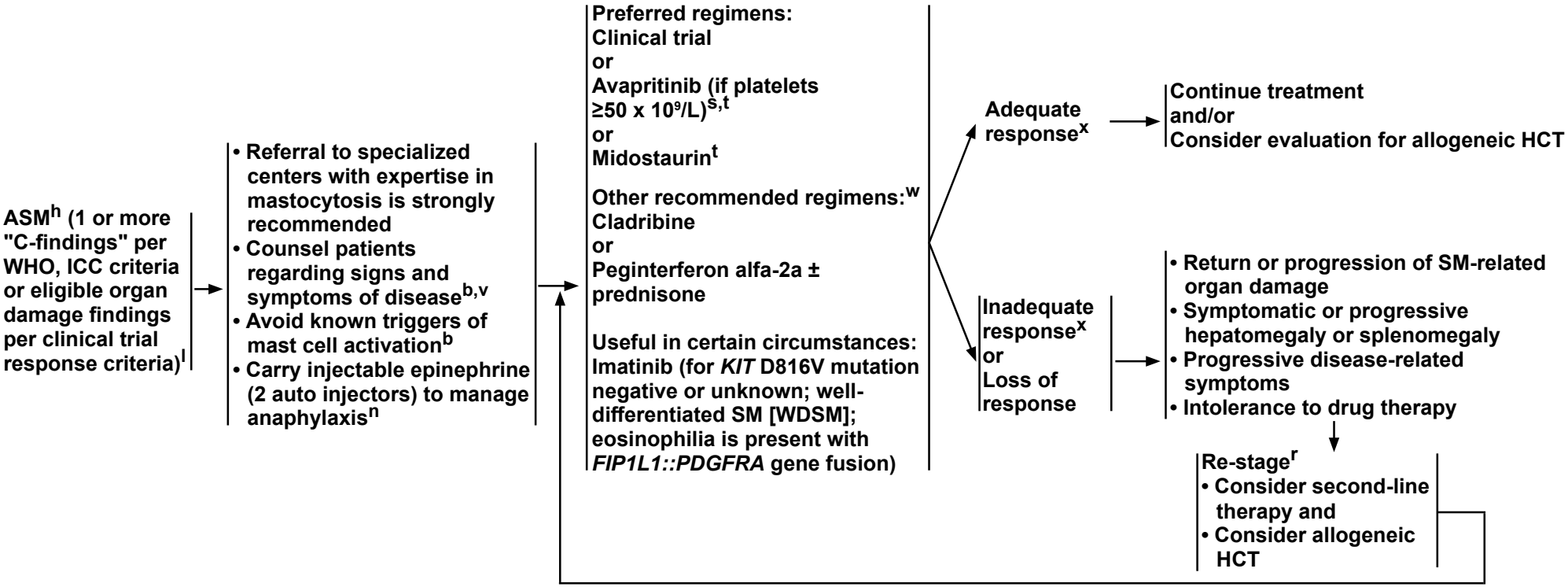
TREATMENT FOR AGGRESSIVE SYSTEMIC MASTOCYTOSIS[k]



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

[h] Diagnostic criteria for the variants of Systemic Mastocytosis (SM-D).

[k] Adverse prognostic variables and risk stratification in Systemic Mastocytosis (SM-I).

[l] IWG-MRT-ECNM and modified IWG-MRT-ECNM criteria are used to establish eligible organ damage findings for clinical trial enrollment and to adjudicate response to therapy. The proposed ECNM-AIM response criteria use the same organ damage to assess response (SM-G). B- and C-findings are used for the diagnosis of the WHO subtype of SM (SM-D, SM-E, SM-F).

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

[r] 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.

[s] Avapritinib is not recommended for the treatment of patients with platelet counts of less than 50 X 10⁹/L.

[t] Refer to the package insert for the full prescribing information, dose modifications, and monitoring for adverse reactions: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

[v] Taylor F, et al. Leuk Res 2021;108:106606.

[w] For patients with advanced SM, cladribine may be particularly useful when rapid debulking of disease is required whereas peginterferon alfa-2a, which has a cytostatic mechanism of action, may be more suitable for patients with slowly progressive disease without the need for rapid cytoreduction.

[x] See organ damage assessment and response criteria (SM-G). Clinical benefit may not reach the threshold of the clinical trial response criteria.

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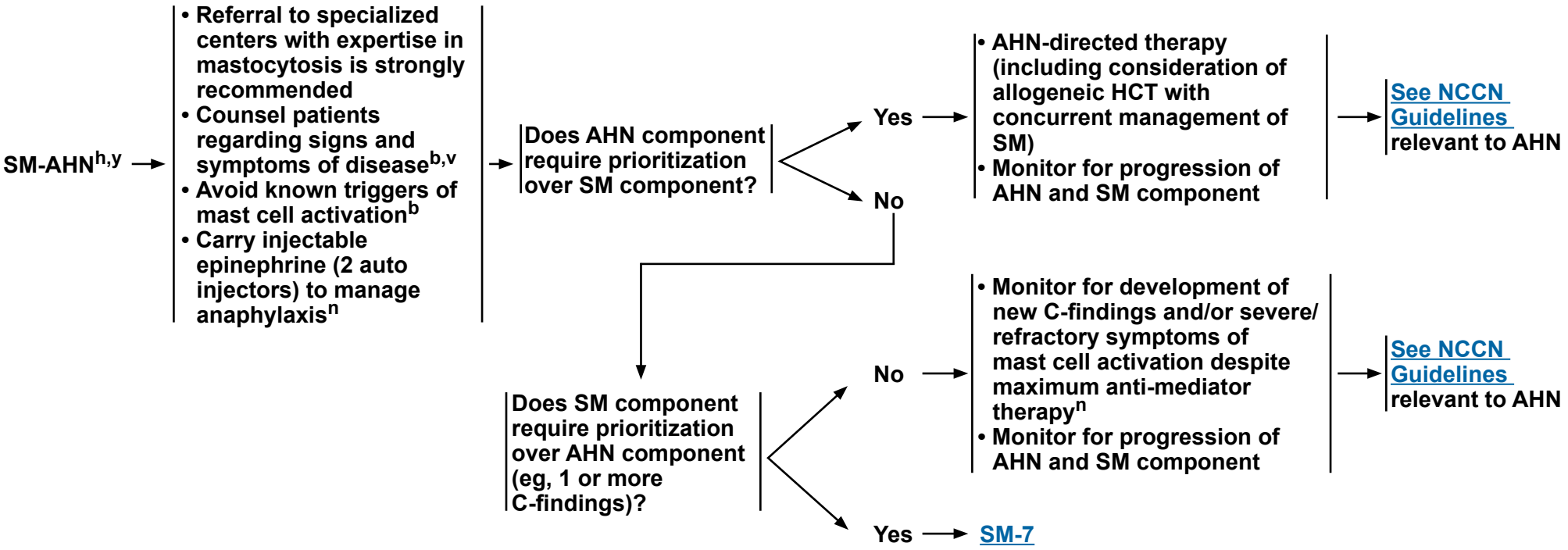
TREATMENT FOR SYSTEMIC MASTOCYTOSIS WITH AN ASSOCIATED HEMATOLOGIC NEOPLASM[k]



[b] Patients should be counseled about the signs/symptoms and potential triggers of mast cell activation (SM-J). Multidisciplinary collaboration with sub-specialists (eg, anesthesia for procedures/surgery; high-risk obstetrics for pregnancy) is recommended (SM-L).
[h] Diagnostic criteria for the variants of Systemic Mastocytosis (SM-D).
[k] Adverse prognostic variables and risk stratification in Systemic Mastocytosis (SM-I).
[n] See SM-K for anti-mediator drug therapy approaches for mast cell activation symptoms.
[v] Taylor F, et al. Leuk Res 2021;108:106606.
[y] These algorithms refer to SM-AHN with myeloid neoplasms, which comprise the majority of cases.

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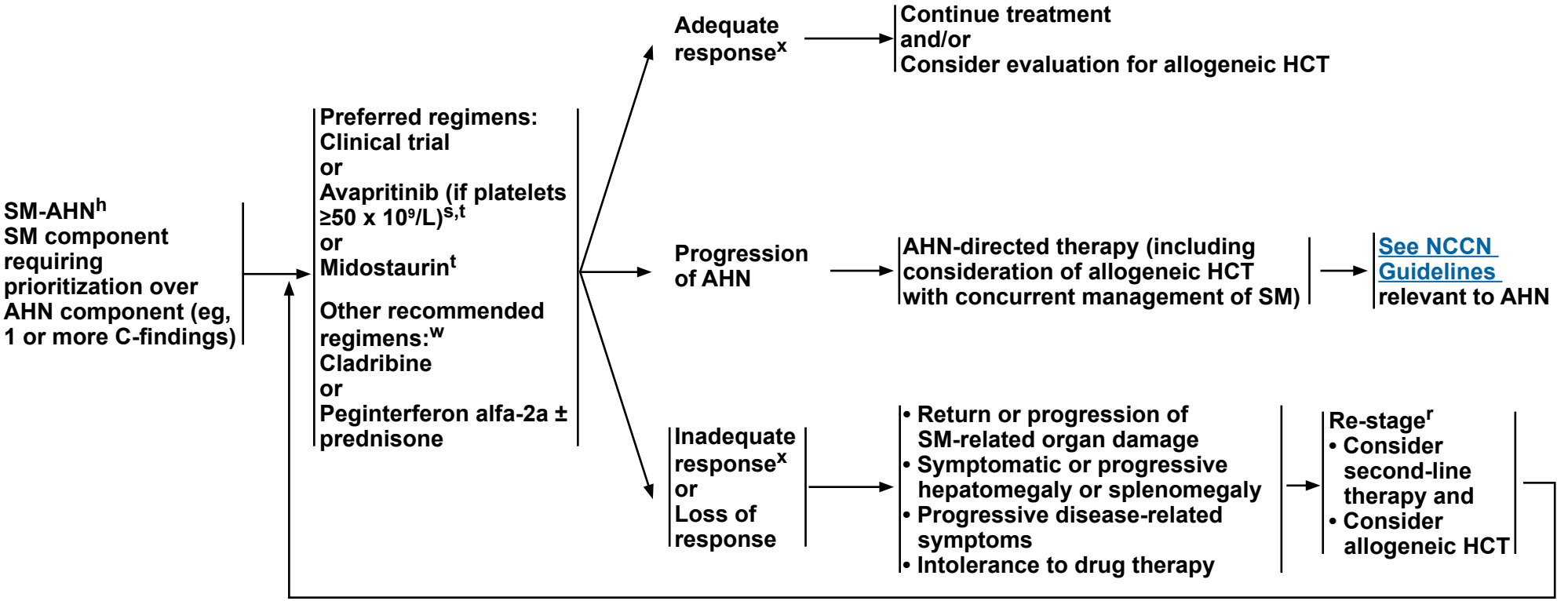
TREATMENT FOR SYSTEMIC MASTOCYTOSIS WITH AN ASSOCIATED HEMATOLOGIC NEOPLASM[k]



[h] Diagnostic criteria for the variants of Systemic Mastocytosis (SM-D).
[k] Adverse prognostic variables and risk stratification in Systemic Mastocytosis (SM-I).
[r] 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.
[s] Avapritinib is not recommended for the treatment of patients with platelet counts of less than 50 X 10^9/L.
[t] Refer to the package insert for the full prescribing information, dose modifications, and monitoring for adverse reactions: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
[w] For patients with advanced SM, cladribine may be particularly useful when rapid debulking of disease is required whereas peginterferon alfa-2a, which has a cytostatic mechanism of action, may be more suitable for patients with slowly progressive disease without the need for rapid cytoreduction.
[x] See organ damage assessment and response criteria (SM-G). Clinical benefit may not reach the threshold of the clinical trial response criteria.

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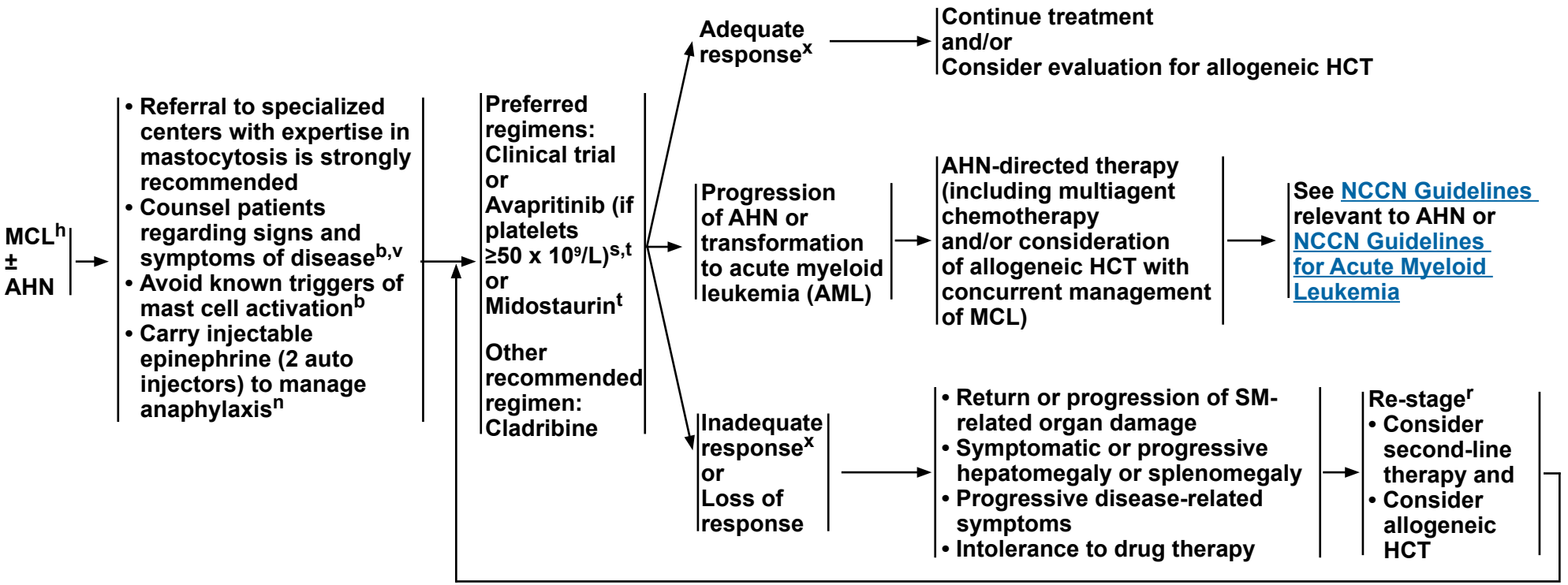
TREATMENT FOR MAST CELL LEUKEMIA ± ASSOCIATED HEMATOLOGIC NEOPLASM[k,z]



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

[h] Diagnostic Criteria for the Variants of Systemic Mastocytosis (SM-D).

[k] Adverse Prognostic Variables and Risk Stratification in Systemic Mastocytosis (SM-I).

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

[r] 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.

[s] Avapritinib is not recommended for the treatment of patients with platelet counts of less than 50 X 10^9/L.

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[v] Taylor F, et al. Leuk Res 2021;108:106606.

[x] See organ damage assessment and response criteria (SM-G). Clinical benefit may not reach the threshold of the clinical trial response criteria.

[z] Patients with chronic MCL have no organ damage. However, treatment should be considered given the poor prognosis of MCL.

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2022 CLASSIFICATION OF MASTOCYTOSIS

WHO 5th Edition[1,a]	International Consensus Classification (ICC)[2]
Cutaneous mastocytosis	
• Urticaria pigmentosa/maculopapular cutaneous mastocytosis	• Urticaria pigmentosa/maculopapular cutaneous mastocytosis
▸ Monomorphic	• Diffuse cutaneous mastocytosis
▸ Polymorphic	• Mastocytoma of skin
• Diffuse cutaneous mastocytosis	
• Cutaneous mastocytoma	
▸ Isolated mastocytoma	
▸ Multilocalized mastocytoma	
Systemic mastocytosis	
• Bone marrow mastocytosis (BMM)[b]	• Indolent SM
• Indolent SM	▸ Bone marrow mastocytosis[b]
• Smoldering SM	• Smoldering SM
• Aggressive SM	• Aggressive SM
• SM with an associated hematologic neoplasm[c]	• SM with an associated myeloid neoplasm (SM-AMN)[c]
• Mast cell leukemia	• Mast cell leukemia
Mast cell sarcoma	

Footnotes

[a] See Discussion for WDSM.

[b] BMM is now considered a separate subtype of SM in the WHO 5th edition classification of haematolymphoid tumours characterized by no mastocytosis skin lesions, no B-findings and basal serum total tryptase level <125 ng/mL, whereas in the ICC it is considered a clinicopathologic variant of ISM.

[c] In the ICC, SM-AHN has been modified such that the AHN is defined as an AMN only.

References

1 Adapted with permission from Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: Myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36:1703-1719.

2 Adapted with permission from Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: Integrating morphologic, clinical and genomic data. Blood 2022;140:1200-1228.

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WHO DIAGNOSTIC CRITERIA FOR CUTANEOUS MASTOCYTOSIS[1,a]

CUTANEOUS MASTOCYTOSIS

Skin lesions demonstrate the typical findings of urticaria pigmentosa/maculopapular CM (which includes telangiectasia macularis eruptiva perstans), diffuse CM, or solitary mastocytoma. This criterion also applies to typical histologic infiltrates of mast cells in both a multifocal dense or diffuse pattern in an adequate skin biopsy. In addition, a diagnostic prerequisite for the diagnosis of CM is the absence of features/ criteria sufficient to establish the diagnosis of SM.

Footnotes

[a] These criteria are the same in the 2022 WHO classification. Khoury JD, et al. Leukemia 2022;36:1703-1719.

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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2022 DIAGNOSTIC CRITERIA FOR SYSTEMIC MASTOCYTOSIS[a,1,2]

Major	**Multifocal dense aggregates of mast cells[b]**
Minor	**• >25% mast cells with atypical morphology[c]** **• *KIT* D816V or other activating *KIT* mutation[d]** **• CD2, CD25, and/or CD30 expression on mast cells[e]** **• Serum total tryptase >20 ng/mL[f]**

WHO 5th Edition[1]	ICC[2,g]
1 major + 1 minor criteria	**1 major criterion**
OR	**OR**
≥3 minor criteria	**≥3 minor criteria**

Footnotes

[a] For updates to SM in the WHO 5th edition, see Khoury JD, et al. Leukemia 2022;36:1703-1719.
[b] According to the WHO and ICC, the major criterion for the diagnosis of SM requires the presence of multifocal dense mast cell (MC) infiltrates (≥15 MCs in aggregates) in bone marrow sections and/or other extracutaneous organ(s). The ICC also requires demonstration of CD117 (often strong) and MC tryptase expression (often weaker and may be partial) to confirm the MC infiltrate. Per the ICC, with the support of IHC, the major criterion on its own can be sufficient for diagnosing SM, when myeloid and/or lymphoid neoplasm with eosinophilia (MLNE) is carefully excluded.
[c] This refers to either >25% of mast cells in bone marrow aspirate smears are immature or atypical in morphologic appearance when compared to a normal MC or >25% of mast cells in a tissue biopsy are spindle-shaped or have atypical morphology. It is preferred that mast cell morphology is assessed in an adequate bone marrow aspirate smear or touch preparation, but in the absence of such then an adequate extracutaneous tissue biopsy may be used.
[d] Any *KIT* mutation that causes ligand-independent activation meets this minor criterion, although this is typically D816V. This can be assessed in bone marrow, peripheral blood, or extracutaneous organs. A high sensitivity PCR assay is recommended for detection of the *KIT* D816V mutation.
[e] CD2, CD25, and/or CD30 expression on mast cells meets this minor criterion, which may be assessed via flow cytometry and/or IHC; discordance between phenotyping techniques may be seen due to different antibody clones or other technical factors. It is recommended that mast cells be confirmed with tryptase and CD117 IHC, recognizing that a small number of SM cases may show dim to negative staining of tryptase in neoplastic mast cells.
[f] Serum total tryptase >20 ng/mL is used as a minor criterion unless an AMN is present. The 5th edition of the WHO Classification of Haematolymphoid Tumours recommends that the serum total tryptase level is adjusted for the presence of HαT. The WHO recommendation is to divide the serum total tryptase level by the number of *TPSAB1* genes + 1. An alternative method to adjust for the basal serum tryptase level in the presence of HαT is available in the online calculator: https://bst-calculater.niaid.nih.gov/. Chovanec J, et al. Blood Adv 2023;7:1796-1810.
[g] The identification of one of the tyrosine kinase gene fusions associated with MLNE excludes a diagnosis of SM. Rare cases with both a gene fusion associated with MLNE and a *KIT* mutation have been reported, and the MLNE represents the AMN.

References

[1] Adapted with permission from El Hussein S, Chifotides HT, Khoury JD, et al. Systemic mastocytosis and other entities involving mast cells: A practical review and update. Cancers (Basel) 2022;14:3474.
[2] Adapted with permission from Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: Integrating morphologic, clinical, and genomic data. Blood 2022;140:1200-1228.

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DIAGNOSTIC CRITERIA FOR THE VARIANTS OF SYSTEMIC MASTOCYTOSIS[1,2]

2017 WHO Diagnostic Criteria

Indolent Systemic Mastocytosis
- Meets the general criteria for SM
- No C-findings[a]
- No evidence of an AHN
- Low mast cell burden
- Skin lesions are frequently present

Bone Marrow Mastocytosis[b]
- As above (ISM), but with bone marrow involvement and no skin lesions

Smoldering Systemic Mastocytosis
- Meets the general criteria for SM
- ≥2 B-findings; no C-findings[a]
- No evidence of an AHN
- High mast cell burden
- Does not meet the criteria for MCL

Systemic Mastocytosis with an Associated Hematologic Neoplasm[c]
- Meets the general criteria for SM
- Meets the criteria for an AHN (ie, a myelodysplastic syndrome [MDS], AML, myeloproliferative neoplasm [MPN], lymphoma, or another hematologic neoplasm classified as a distinct entity in the WHO classification)

Aggressive Systemic Mastocytosis[a]
- Meets the general criteria for SM
- ≥1 C-finding[d]
- Does not meet the criteria for MCL
- Skin lesions are usually absent

Mast Cell Leukemia
- Bone marrow aspirate smears show ≥20% mast cells[e]
- In classic cases, mast cells account for ≥10% of the peripheral blood white blood cells, but the aleukemic variant (in which mast cells account for <10%) is more common
- Mast cell variants include:
  - Acute MCL [≥1 C-finding(s)] vs. chronic MCL (no C-findings)
  - MCL with an AHN vs. MCL without an AHN
  - Primary (de novo) vs. secondary MCL (arising from another SM variant)
- Skin lesions are usually absent

Footnotes

[a] ASM with 5%–19% mast cells in bone marrow aspirate is referred to as ASM in transformation (ASM-t).

[b] In the 2022 WHO classification, BMM is a separate category from ISM but in the ICC classification, it is a subvariant of ISM. Khoury JD, et al. Leukemia 2022;36:1703-1719. Arber DA, et al. Blood 2022;140:1200-1228.·

[c] In the 2022 ICC classification, this is listed as SM with an AMN. Arber DA, et al. Blood 2022;140:1200-1228.

[d] B- and C-findings indicate organ involvement without and with organ dysfunction, respectively. See criteria for B-findings (SM-E) and C-findings (SM-F) in patients with systemic mastocytosis.

[e] Atypical immature mast cells include promastocytes, metachromatic blast-like cells, or highly pleomorphic mast cells. Thus, the ICC restricts MCL to “acute” MCL which presents with C-findings. For example “chronic” MCL which is typically seen with spindle-shaped mast cells would not be included in this definition. The ICC also notes that in the presence of an inadequate aspirate smear, MCL may be diagnosed by a diffuse, dense infiltration of atypical immature mast cells on bone marrow biopsy.

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.

[2] Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: Myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36:1703-1719.

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CRITERIA FOR B-FINDINGS IN PATIENTS WITH SYSTEMIC MASTOCYTOSIS[a]

WHO[1]	ICC[2]
• >30% mast cells on bone marrow biopsy and serum total tryptase >200 ng/mL	• >30% mast cells on bone marrow biopsy and serum total tryptase >200 ng/mL
• Signs of dysplasia or myeloproliferation in non-mast cell lineage, but criteria not met for a WHO AHN, with normal or only slightly abnormal blood counts	• Cytopenia not meeting criteria for C-findings or -cytosis. Reactive causes are excluded and criteria for myeloid neoplasms are not met.
• Hepatomegaly without impaired liver function, palpable splenomegaly without hypersplenism and/or lymphadenopathy (palpation or imaging)	• Hepatomegaly without impaired liver function, palpable splenomegaly without hypersplenism and/or lymphadenopathy >1 cm (palpation or imaging)

Addition in the WHO 5th Edition[3]
• *KIT* D816V variant allele frequency ≥10%

Footnotes

[a] In patients with SM in whom less than 2 B-findings and no C-findings are detected, the diagnosis is ISM. The diagnosis of BMM requires no B- or C-findings. When 2 or more B-findings but no C-findings are present, the diagnosis is SSM. When 1 or more C-findings (with or without additional B-findings) are detected, the final diagnosis is ASM (<20% MCs in bone marrow 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.

[2] Adapted with permission from Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: Integrating morphologic, clinical, and genomic data. Blood 2022;140:1200-1228.

[3] Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: Myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36:1703-1719.

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CRITERIA FOR C-FINDINGS IN PATIENTS WITH SYSTEMIC MASTOCYTOSIS[a,1]

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, hemoglobin level <10 g/dL, and/or platelet count <100 x 10^9/L**
- **Palpable splenomegaly with hypersplenism**
- **Skeletal involvement, with large osteolytic lesions (if the size of the lesion is ≥2 cm, it is considered large) with or without pathologic fractures (pathologic fractures caused by osteoporosis do not qualify as a C-finding). Small osteolytic and/or sclerotic lesions do not define advanced SM.**
- **Palpable hepatomegaly with impairment of liver function, and/or ascites, and/or portal hypertension**
- **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, the diagnosis is ISM. The diagnosis of BMM requires no B- or C-findings. When 2 or more B-findings but no C-findings are present, the diagnosis is SSM. When 1 or more C-findings (with or without additional B-findings) are detected, the final diagnosis is ASM (<20% MCs in bone marrow 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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ORGAN DAMAGE ASSESSMENT AND RESPONSE CRITERIA

International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis (IWG-MRT-ECNM) and modified IWG-MRT-ECNM criteria are used to establish eligible organ damage findings for clinical trial enrollment and to adjudicate response to therapy. The proposed European Competence Network on Mastocytosis-American Initiative in Mast Cell Diseases (ECNM-AIM) response criteria use the same organ damage to assess response.

IWG-MRT:
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 response criteria in advanced systemic mastocytosis. Blood 2013;121:2393-2401.

Modified IWG:
Shomali W, Gotlib J. Response criteria in advanced systemic mastocytosis: Evolution in the era of KIT inhibitors. Int J Mol Sci 2021;22:2983.

ECNM-AIM
Gotlib J, Schwaab J, Shomali W, et al. Proposed European Competence Network on Mastocytosis-American Initiative in Mast Cell Diseases (ECNM-AIM) response criteria in advanced systemic mastocytosis. J Allergy Clin Immunol Pract 2022;10:2025-2038.e1.

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RECOMMENDATIONS FOR HISTOPATHOLOGY ANALYSIS AND *KIT* D816V MUTATION TESTING

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 pathology of mast cell diseases.**
- **The peripheral blood smear should be reviewed for the presence of mast cells (eg, MCL) and/or for evidence of an AHN (dysplasia, monocytosis, and/or eosinophilia). The percentage of circulating mast cells should be reported in patients with MCL (eg, ≥10% vs. <10% mast cells [aleukemic variant]).**
- **Bone marrow aspirate and biopsy should include comment on the percentage of neoplastic mast cells, and their morphology (spindle-shaped, well-differentiated [resembling normal mast cells],[a] 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 (1–2 cm) analysis should include comment on the percent mast cell burden and morphology of mast cells in biopsy (eg, multifocal dense infiltrates [a major diagnostic criterion] or a primarily interstitial pattern of involvement). In patients with a primarily interstitial pattern of mast cells, peripheral blood eosinophilia, and negativity for *KIT* D816V mutation, then the *FIP1L1::PDGFRA* gene fusion should be tested.**
- **On the core biopsy, IHC with markers for mast cell tryptase, CD117, CD25, and CD30 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. CD34 staining may also be obtained to quantify whether the proportion of myeloblasts is increased, especially in SM-AHN, eg, SM associated with MDS; MPN; MDS/MPN; chronic eosinophilic leukemia, not otherwise specified; 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 >ISM/SSM, particularly in areas of mast cell aggregates.**
- **Flow cytometry is a complementary tool in the diagnosis or monitoring of mast cell disease. CD117, CD25, CD30, and CD2 are standard flow markers. 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 SM, especially in patients 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 alone are not recommended for the detection of *KIT* D816V. NGS assays can exhibit low sensitivity and higher-sensitivity assays should always be performed.**

KIT D816V Mutation Testing on SM-H 2 of 3

[a] WDSM is a morphologic variant present in all subtypes of SM.

References on SM-H 3 of 3

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RECOMMENDATIONS FOR HISTOPATHOLOGY ANALYSIS AND *KIT* D816V MUTATION TESTING

KIT D816V MUTATION TESTING[4]

- **If a diagnosis of SM is suspected, molecular testing for *KIT* D816V using an assay with high sensitivity (eg, ASO-qPCR or digital droplet PCR)[b,5] 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. Fresh bone marrow aspirate is preferable, but formalin-fixed paraffin-embedded tissue can also be used. Decalcified tissue typically interferes with DNA/RNA assays, and thus, decalcified bone marrow should not be used for mutational analysis. If initial screening of the peripheral blood does not detect the *KIT* D816V mutation in a patient with suspected SM, testing of the bone marrow should be undertaken with a highly sensitive assay (eg, ASO-qPCR or digital droplet PCR).**
- **When applied to the bone marrow, these assays can detect the *KIT* D816V mutation in >95% 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, or others) or in other regions of *KIT* that are not detectable by high-sensitivity assays (eg, ASO-qPCR or digital droplet PCR). 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 (eg, ASO-qPCR or digital droplet PCR), 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 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 high-sensitivity assays (eg, ASO-qPCR or digital droplet PCR) on DNA or on RNA/ complementary DNA should be considered before initiating therapy and serially during therapy.**

[b] In the absence of a highly sensitive quantitative PCR assay, qualitative PCR can be used.

References on SM-H 3 of 3

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RECOMMENDATIONS FOR HISTOPATHOLOGY ANALYSIS AND *KIT* D816V MUTATION TESTING

REFERENCES

[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.
[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;29:1223-1232.
[5] Greiner G, Gurbisz M, Ratzinger F, et al. Digital PCR: A sensitive and precise method for *KIT* D816V quantification in mastocytosis. Clin Chem 2018;64:547-555.

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ADVERSE PROGNOSTIC VARIABLES AND RISK STRATIFICATION IN SYSTEMIC MASTOCYTOSIS

ADVERSE PROGNOSTIC VARIABLES IN SYSTEMIC MASTOCYTOSIS (SM-I, 2 of 5)

RISK STRATIFICATION FOR PATIENTS WITH SYSTEMIC MASTOCYTOSIS

MARS	**(SM-I, 3 of 5)**
MAPS	**(SM-I, 3 of 5)**
IPSM	**(SM-I, 4 of 5)**
GPSM	**(SM-I, 5 of 5)**

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ADVERSE PROGNOSTIC VARIABLES IN SYSTEMIC MASTOCYTOSIS

Clinical/Laboratory Variables

- **WHO subclassification of SM[1]**
- **Advanced age, history of weight loss, anemia, thrombocytopenia, hypoalbuminemia, and excess bone marrow blasts (>5%)[1]**
- **Eosinophilia[2,3,a]**
- **Splenomegaly[4]**
- **Increased alkaline phosphatase[4]**

Cytogenetic/Molecular Variable

- **Poor-risk karyotype (monosomy 7 or complex karyotype)[5]**
- **Multilineage involvement of *KIT* D816V mutation[6]**
- **Number of non-*KIT* D816V mutations[7]**
- ***SRSF2/ASXL1/RUNX1* (S/A/R), and/or *EZH2* or *ASXL1/CBL* mutation profile[4,5,7-10]**

Footnotes

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

References

[1] Lim KH, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood 2009;113:5727-5736.
[2] 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.
[3] Kluin-Nelemans HC, Reiter A, Illerhaus A, et al. Prognostic impact of eosinophils in mastocytosis: analysis of 2350 patients collected in the ECNM Registry. Leukemia 2020;34:1090-1101.
[4] 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.
[5] Naumann N, Jawhar M, Schwaab J, et al. Incidence and prognostic impact of cytogenetic aberrations in patients with systemic mastocytosis. Genes Chromosomes Cancer 2018;57:252-259.
[6] 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.
[7] Schwaab J, Schnittger S, Sotlar K, et al. Comprehensive mutational profiling in advanced systemic mastocytosis. Blood 2013;122:2460-2466.
[8] 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.
[9] 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.
[10] Muñoz-González JI, Jara-Acevedo M, Alvarez-Twose I, et al. Impact of somatic and germline mutations on the outcome of systemic mastocytosis. Blood Adv 2018;2:2814-2828.

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RISK STRATIFICATION FOR PATIENTS WITH SYSTEMIC MASTOCYTOSIS

MUTATION-ADJUSTED RISK SCORE (MARS) FOR ADVANCED SYSTEMIC MASTOCYTOSIS[11]

Prognostic Variable	Points
Age >60 years	1
Hemoglobin <10 g/dL	1
Platelets <100 x 10^9/L	1
One S/A/R (*SRSF2, ASXL1, or RUNX1*) mutation	1
≥2 S/A/R mutation	2

Risk Group	Points
Low	0 to 1
Intermediate	2
High	3 or 5

MAYO ALLIANCE PROGNOSTIC SYSTEM (MAPS) FOR MASTOCYTOSIS[12]

Prognostic Variable	Points
Age >60 years	1
Advanced SM vs. ISM/SSM	2
Platelets <150 x 10^9/L	1
Serum alkaline phosphatase (ALP) > normal range	1
Adverse mutation (*ASXL1*, *RUNX1*, and *NRAS*)	1

Risk Group	Points
Low	≤2
Intermediate-1	3
Intermediate-2	4
High	≥5

[11] Jawhar M, Schwaab J, Alvarez-Twose I, et al. MARS: Mutation-Adjusted Risk Score for Advanced Systemic Mastocytosis. J Clin Oncol 2019;37:2846-2856.
[12] Pardanani A, Shah S, Mannelli F, et al. Mayo alliance prognostic system for mastocytosis: clinical and hybrid clinical-molecular models. Blood Adv 2018;2:2964-2972.

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RISK STRATIFICATION FOR PATIENTS WITH SYSTEMIC MASTOCYTOSIS

INTERNATIONAL PROGNOSTIC SCORING SYSTEM FOR MASTOCYTOSIS (IPSM) SCORE FOR NON-ADVANCED SYSTEMIC MASTOCYTOSIS[13]

Prognostic Variable	Points
Age ≥60 years	1
Alkaline phosphatase ≥100 U/L	1

Risk Group	Points
Low-risk	0
Intermediate-risk group 1 (Int-1)	1
Intermediate-risk group 2 (Int-2)	2

IPSM SCORE FOR ADVANCED SYSTEMIC MASTOCYTOSIS[13]

Prognostic Variable	Points
Age ≥60 years	1
Tryptase ≥125 ng/mL	1
Leukocytes ≥16 × 10^9/L	1
Hemoglobin ≤11 g/dL	1
Platelets ≤100 x 109/L	1
Skin involvement	-1

Risk Group	Points
Advanced SM 1 (AdvSM-1)	-1 to 0
Advanced SM 2 (AdvSM-2)	1
Advanced SM 3 (AdvSM-3)	2–3
Advanced SM 4 (AdvSM-4)	4 or 5

[13] Sperr WR, Kundi M, Alvarez-Twose I, et al. International prognostic scoring system for mastocytosis (IPSM): a retrospective cohort study. Lancet Haematol 2019;6:e638-e649.

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RISK STRATIFICATION FOR PATIENTS WITH SYSTEMIC MASTOCYTOSIS

GLOBAL PROGNOSTIC SCORE MODEL FOR PROGRESSION-FREE SURVIVAL (GPSM-PFS)[14]

Prognostic Variable	Points
Hemoglobin ≤11 g/dL	-
Platelet count ≤100 x 10^9/L	1
Serum alkaline phosphatase ≥140 IU/L	-
Serum baseline tryptase ≥125 µg/L	2
Serum β2-microglobulin ≥2.5 µg/mL	3.5
Presence of *SRSF2*, *ASXL1*, *RUNX1*, *DNMT3A* gene mutations	-

Risk Group	Points
Low risk	0
Intermediate risk	1–3.5
High risk	>3.5

GLOBAL PROGNOSTIC SCORE MODEL FOR OVERALL SURVIVAL (GPSM-OS)[14]

Prognostic Variable	Points
Hemoglobin ≤11 g/dL	1
Platelet count ≤100 x 10^9/L	-
Serum alkaline phosphatase ≥140 IU/L	1.5
Serum baseline tryptase ≥125 µg/L	-
Serum β2-microglobulin ≥2.5 µg/mL	-
Presence of *SRSF2*, *ASXL1*, *RUNX1*, *DNMT3A* gene mutations	1

Risk Group	Points
Low risk	0
Intermediate risk	1–1.5
High risk	≥2

[14] Muñoz-González JI, Álvarez-Twose I, Jara-Acevedo M, et al. Proposed global prognostic score for systemic mastocytosis: a retrospective prognostic modelling study. The Lancet Haematol 2021;8:e194-e204.

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

- **Anaphylaxis**
- **Fatigue**
- **Light-headedness, syncope/fainting**
- **Skin:**
  - **Flushing of the face, neck, and chest**
  - **Pruritus, itching, +/- rash**
  - **Hives, with or without angioedema (swelling) skin rashes**
- **Gastrointestinal:**
  - **Gastric distress, diarrhea, nausea, vomiting, abdominal pain, bloating, gastroesophageal reflux disease**
- **Neuropsychiatric symptoms**
  - **Headache and/or brain fog, cognitive dysfunction, anxiety, depression, short memory span, inability to concentrate**
- **Cardiovascular:**
  - **Rapid heart rate, chest pain**
  - **Low blood pressure, high blood pressure at the start of a reaction, blood pressure instability**
- **Pulmonary:**
  - **Wheezing and shortness of breath**
- **Musculoskeletal:**
  - **Bone/muscle pain, osteosclerosis, osteopenia, osteoporosis, focal bone pain concerning for fractures**
- **Nasal/throat:**
  - **Nasal itching and congestion**
  - **Throat itching and swelling**

POTENTIAL TRIGGERS OF MAST CELL ACTIVATION

- **Heat, cold, or sudden temperature changes**
- **Sun/sunlight**
- **Natural and chemical odors**
- **Food or beverages, including alcohol**
- **Insect stings**
- **Venoms (eg, hymenoptera, spiders, fire ants, jellyfish, snakes)**
- **Infections (viral, bacterial, or fungal)**
- **Stress: emotional; physical, including pain; or environmental (eg, weather changes, pollution, pollen, pet dander)**
- **Lack of sleep/sleep deprivation**
- **Exercise**
- **Drugs (ie, opioids, nonsteroidal anti-inflammatory drugs, some antibiotics [eg, vancomycin, quinolones, some local/general anesthetics]) and contrast dyes**
- **Vaccinations**
- **Mechanical irritation, friction, or vibration**
- **Surgery**
- **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 MMAS. See Discussion.
[b] From The Mastocytosis Society website: https://tmsforacure.org/symptoms/symptoms-and-triggers-of-mast-cell-activation/

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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

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, or air conditioning
  - Avoid dryness of skin
  - Avoid rubbing

Skin Care
- Take steps to avoid dryness of skin
- Use skin moisturizer
- Topical cromolyn sodium (cream/ointment 1%–4%):[c] apply two to four times a day for urticaria, pruritus, vesicles, or bullae. Do not use on denuded lesions (consider topical antibiotics).
- Topical corticosteroids
- Diffuse lesions: apply bath or sterile gauze with zinc sulfate

Solitary Mastocytoma
- Topical cromolyn sodium (cream/ointment 1%–4%)[c]
- Topical corticosteroid
- Avoid friction and pressure
- Consider surgical excision (ie, flexures, soles, palms, scalp)

Urticaria Pigmentosa and Other Forms
- Trigger(s)-related symptoms
  - Avoidance of triggers
  - Non-sedating H1 antihistamines[d]
  - H2 antihistamines[d]
  - Topical cromolyn sodium (cream/ointment 1%–4%)[c]
- Continuous moderate symptoms
  - Scheduled non-sedating H1 antihistamines[d]
    - ◊ Add sedating H1 antihistamines[d] on demand
  - Scheduled or on-demand H2 antihistamines[d]
  - Scheduled topical cromolyn sodium (cream/ointment 1%–4%)[c]
- Severe symptoms
  - Scheduled non-sedating H1 antihistamines[d]
  - Scheduled sedating H1 antihistamines[d]
  - Scheduled H2 antihistamines[d]
  - Add anti-leukotrienes in patients with refractory disease cases

Diffuse Forms with Life-Threatening Mast Cell-Mediated Related Symptoms, Bullae, and Blistering
- Treatment may require hospitalization
- Sterile conditions
- Topical cromolyn sodium (cream/ointment 1%–4%)[c]
- Topical corticosteroids
- Zinc sulfate
- Oral corticosteroids

[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 MMAS. See Discussion.
[b] Castells M, Butterfield J. Mast cell activation syndrome and mastocytosis: Initial treatment options and long-term management. J Allergy Clin Immunol Pract 2019;4:1097-1106.
[c] Available as a compounded agent.
[d] First-generation anticholinergic antihistamines are not recommended in adult patients >65 years of age.

Continued

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

Organ Involvement/Symptoms	Stepwise Treatment[e,f]
Skin: **Pruritus, flushing, urticaria, angioedema dermatographism**	1. H1 blockers and H2 blockers 2. Leukotriene receptor antagonist 3. Aspirin 4. Ketotifen[c] 5. Topical cromolyn sodium (cream/ointment 1%–4%)[c]
Gastrointestinal: **Diarrhea, abdominal cramping, nausea, vomiting**	1. H2 blockers 2. Cromolyn sodium 3. Proton pump inhibitors 4. Leukotriene receptor antagonist 5. Ketotifen[c]
Neurologic: **Headache, poor concentration and memory, brain fog**	1. H1 blockers and H2 blockers 2. Cromolyn sodium 3. Aspirin 4. Ketotifen[c]
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

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

Continued

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

Indication	Treatment
Systemic hives	Antihistamines (H1 blockers and H2 blockers)
Systemic hives + second organ involved in an acute onset reaction (eg, upper/lower airway, gastrointestinal, neurologic, cardiovascular)	Epinephrine intramuscular (IM) (repeat up to 3 times every 5 minutes in the absence of clinical improvement) IV Epinephrine after 3 doses of epinephrine IM
Acute onset of anaphylaxis with the following symptoms: • Hypotension • Laryngeal edema • Vasomotor collapse • Oxygen desaturation • Seizures	Epinephrine (IM) (repeat up to 3 times every 5 minutes in the absence of clinical improvement) IV Epinephrine after 3 doses of epinephrine IM
Complementary treatments (in addition to antihistamines) • IV fluids • Oxygen • Consider glucagon (if anaphylaxis related to β-adrenergic receptor blockade) • Antihistamines such as diphenhydramine (25 mg every 2–4 h up to 100 mg/24 h) should be considered in conjunction with corticosteroid therapy • Corticosteroids (0.5–1 mg/kg) • 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[8-10]

Continued

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TREATMENT FOR OSTEOPENIA/OSTEOPOROSIS[11,12]

- **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)**
- **Peginterferon alfa-2a**
  - **Consider for patients with refractory bone pain and/or worsening bone mineral density on bisphosphonate therapy**
- **Anti-RANKL monoclonal antibody (eg, denosumab[g])**
  - **Generally used as second-line therapy for patients with bone pain not responding to bisphosphonates or for patients who are not candidates for bisphosphonates because of renal insufficiency**
- **Vertebroplasty/kyphoplasty for refractory pain associated with vertebral compression fractures in selected patients**

Footnotes
[g] An FDA-approved biosimilar is an appropriate substitute.

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SPECIAL CONSIDERATIONS FOR THE COMPREHENSIVE CARE OF PATIENTS WITH SYSTEMIC MASTOCYTOSIS

Surgery[1-5]

- **Risk of anaphylaxis in the perioperative period is estimated to be higher in patients with SM relative to 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[a] (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 iodine).**
- **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 symptom onset.[b] 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).**
- **Carry two epinephrine auto-injectors. Use an H1 blocker 1 hour before receiving a vaccine. Following vaccination, patients should be observed for 60 minutes.[6]**

[a] First-generation anticholinergic antihistamines are not recommended in adult patients >65 years of age.
[b] If baseline tryptase level is available, the formula "1.2X + 2 ng/mL" can be applied to see if an elevation has occurred within the context of mast cell activation.

Continued

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SPECIAL CONSIDERATIONS FOR THE COMPREHENSIVE CARE OF PATIENTS WITH SYSTEMIC MASTOCYTOSIS

Pregnancy[7-15]

- **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-L 3 of 4).**
- **During pregnancy, for patients with severe SM refractory to conventional therapy, cytoreductive therapy with peginterferon alfa-2a is an option. Use of cladribine or tyrosine kinase inhibitors (eg, imatinib, midostaurin, avapritinib) is not recommended. There are not sufficient data to establish the use of peginterferon alfa-2a in pregnancy. It should be used only if benefits outweigh potential risk to the fetus.**

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SPECIAL CONSIDERATIONS FOR THE COMPREHENSIVE CARE OF PATIENTS WITH SYSTEMIC MASTOCYTOSIS[c]

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

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

[c] Kar S, Krishnan A, Preetha K, Mohankar A. A review of antihistamines used during pregnancy. J Pharmacol Pharmacother 2012;3:105-108.
[d] Breastfeeding by patients with SM should be done in consultation with a pediatrician and International Board Certified Lactation Consultant (IBCLC).

Continued

Note: All recommendations are category 2A unless otherwise indicated.
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SPECIAL CONSIDERATIONS FOR THE COMPREHENSIVE CARE OF PATIENTS WITH SYSTEMIC MASTOCYTOSIS[c]

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

Group	Medication	Pregnancy Implications	Lactation Implications
Glucocorticoids	Hydrocortisone	Increased risk of oral clefts with use in the first trimester	Excreted in breast milk, wait 4 h after dose
	Prednisone	Increased risk of oral clefts with use in the first trimester	Excreted in breast milk
	Betamethasone	Increased risk of oral clefts with use in the first trimester, nonfluorinated corticosteroid preferred	Excreted in breast milk, wait 4 h after dose
	Dexamethasone	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	No increased risk of birth defects	Unknown if excreted into breast milk, use with caution
Cytoreductive therapies	Cladribine	Teratogenic effects and fetal mortality observed	Not recommended
	Imatinib	Pregnancy not recommended within 2 wk of last imatinib dose	Not recommended
	Peginterferon alfa-2a	There are limited data regarding the use of peginterferon-alfa-2a in pregnancy	There are limited data regarding the use of peginterferon-alfa-2a in pregnancy

[c] Kar S, Krishnan A, Preetha K, Mohankar A. A review of antihistamines used during pregnancy. J Pharmacol Pharmacother 2012;3:105-108.
[d] Breastfeeding by patients with SM should be done in consultation with a pediatrician and IBCLC.

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ABBREVIATIONS

AHN	associated hematologic neoplasm
ALP	alkaline phosphatase
AML	acute myeloid leukemia
AMN	associated myeloid neoplasm
ASM	aggressive systemic mastocytosis
ASM-t	aggressive systemic mastocytosis in transformation
ASO-qPCR	allele-specific oligonucleotide quantitative reverse transcriptase polymerase chain reaction
BMM	bone marrow mastocytosis
CBC	complete blood count
CM	cutaneous mastocytosis
DEXA	dual-energy x-ray absorptiometry
ECNM-AIM	European Competence Network on Mastocytosis-American Initiative in Mast Cell Diseases
FISH	flurouresence in situ hybridization
GPSM	Global Prognostic Score Model
GPSM-OS	Global Prognostic Score Model for overall survival
GPSM-PFS	Global Prognostic Score Model for progression-free survival
H&P	history and physical
HCT	hematopoietic cell transplant
HαT	hereditary alpha-tryptasemia
HLA	human leukocyte antigen
IBCLC	International Board Certified Lactation Consultant
ICC	International Consensus Classification
IHC	immunohistochemistry
IM	intramuscular
IPSM	International Prognostic Scoring System for Mastocytosis
ISM	indolent systemic mastocytosis
IWG-MRT-ECNM	International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis
LDH	lactate dehydrogenase
LFT	liver function test
MAPS	Mayo Alliance Prognostic System
MARS	Mutation-Adjusted Risk Score
MC	mast cell
MCAS	mast cell activation syndrome
MCL	mast cell leukemia
MLNE	myeloid and/or lymphoid neoplasm with eosinophilia
MMAS	monoclonal mast cell activation syndrome
MPN	myeloproliferative neoplasm(s)
MQLQ	Mastocytosis Quality of Life Questionnaire
MSAF	Mastocytosis Symptom Assessment Form
NGS	next-generation sequencing
PCR	polymerase chain reaction
QOL	quality of life
SM	systemic mastocytosis
SM-AHN	systemic mastocytosis with an associated hematologic neoplasm
SSM	smoldering systemic mastocytosis
WDSM	well-differentiated systemic mastocytosis

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.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2024
Systemic Mastocytosis

Discussion

This discussion corresponds to the NCCN Guidelines for Systemic Mastocytosis. Last updated: April 24, 2024.

Table of Contents

Overview

Mastocytosis is a group of heterogeneous disorders resulting from the clonal growth of abnormal mast cells and their accumulation in the skin and/or in extracutaneous organs.[1] In the revised 2017 WHO classification, mastocytosis was removed as one of the subtypes of myeloproliferative neoplasms (MPN) and has since been listed as a separate disease entity with its own distinctive clinical and pathologic features.[2] 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 comprehensive care of patients with mastocytosis requires a multidisciplinary team approach (involving dermatologists, hematologists, pathologists, gastroenterologists, allergists, and immunologists), preferably in specialized centers with expertise in the treatment of patients with mast cell disorders.[4-6] The identification of *KIT* D816V mutation and the emergence of new targeted therapies have significantly improved the diagnosis and treatment of SM.[6-8] However, certain aspects of clinical care, particularly the diagnosis, assessment, and management of mast cell activation symptoms, continue to present challenges.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Systemic Mastocytosis provide recommendations for the diagnosis and comprehensive care of patients with SM. Management of CM is not included in these guidelines. Referral to centers with expertise in mastocytosis is strongly recommended.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of this version of the NCCN Guidelines® for Systemic Mastocytosis, an electronic search of the PubMed database was performed to obtain key literature in Systemic Mastocytosis published since the previous Guidelines update using the following search term: systemic mastocytosis. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[9]

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; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines as discussed by the panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[10] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead

focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Diagnostic Classification

Cutaneous Mastocytosis

The diagnosis of CM requires the presence of clinical and histopathologic 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 subvariants: urticaria pigmentosa (UP)/maculopapular cutaneous mastocytosis (MPCM), diffuse CM, and mastocytoma of the skin.[11]

Systemic Mastocytosis

In 2022, the International Consensus Classification (ICC)[12] and a 5th edition of the WHO Classification[13] generated modifications to the diagnostic criteria for SM. Diagnostic criteria include one major diagnostic criterion (multifocal, dense infiltrates of tryptase and/or CD117-positive mast cells [≥15 mast cells in aggregates] detected in the biopsy sections of bone marrow and/or extracutaneous organs) and four minor diagnostic criteria (the presence of 25% of more mast cells with atypical morphology in lesional tissues; the presence of *KIT* D816V or other activating *KIT* mutation; the aberrant expression of CD2, CD25, and/or CD30 on neoplastic mast cells; and a serum tryptase level >20 ng/mL) in the absence of an associated myeloid neoplasm (AMN). In the ICC, in cases where an aspirate is a dry tap and unevaluable, mast cell leukemia (MCL) may be diagnosed on a core biopsy if a diffuse mast cell infiltrate is present.

In the WHO diagnostic criteria, 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.[14] This is similar for the ICC diagnostic criteria; however, the presence of one major criterion is enough for a diagnosis of SM. If the major criterion is not met, then at least three minor criteria are required.[12] In the 2022 WHO classification, SM is further divided into six different subvariants (based on the mast cell burden, organ involvement, and SM-related organ damage).[13]

- Indolent SM (ISM)
- Bone marrow mastocytosis (BMM)
- Smoldering SM (SSM)
- Aggressive SM (ASM)
- SM with an associated hematologic neoplasm (SM-AHN)
- Mast cell leukemia (MCL)

Dividing SM into subclassifications has been validated in a number of studies.[15-17] In the ICC classification, BMM is considered a clinicopathologic variant of ISM.[12] The associated hematologic neoplasm (AHN) terminology is changed to AMN, reflecting the fact that almost all of these concurrent neoplasms exhibit a myeloid phenotype. The diagnostic criteria for variants of SM are outlined in *Diagnostic Criteria for Variants of Systemic Mastocytosis.*

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 or that have juxtamembrane or transmembrane *KIT* mutations (exons 10–11) and low or absent CD25 expression.[18] 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 (ASM, SM-AHN, and MCL). WDSM has a female predominance and may have a cutaneous onset in childhood. The presence of exon 10 or 11 mutations or lack of the *KIT* D816V mutation may increase the potential for responsiveness to treatment with imatinib.[19-21] An increased expression of CD30 along with the absence of CD25 may be useful in the diagnosis of WDSM and aid in its distinction from other subtypes of SM.[18,22]

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 and can be divided into primary, secondary, and idiopathic.[23-26] Primary MCAS is also referred to as monoclonal mast cell activation syndrome (MMAS).

MCAS is not considered a subtype of SM, but mast cell activation (mediator) symptoms may still occur. MCAS is not associated with an overproliferation of cells and is not considered a prediagnostic condition that ultimately progresses to SM. Basic defining criteria of MCAS include: 1) episodic symptoms consistent with mast cell mediator release affecting greater than or equal to two 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 serum tryptase level (which is the marker of choice).[25]

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 MCAS caused by allergies, drugs, connective tissue disorders, infections, 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.

Hereditary alpha-tryptasemia

Some patients with mediator symptoms, including anaphylaxis, have been diagnosed with hereditary alpha-tryptasemia (HαT), a multisystem disorder characterized by duplications and triplications in the *TPSAB1* gene encoding α-tryptase. This condition is associated with elevation of the basal serum tryptase (a minimum value of 8 ng/mL, although normal, may be found in these patients) as well as symptoms including cutaneous flushing and pruritus, dysautonomia, functional gastrointestinal symptoms, chronic pain, and connective tissue abnormalities, including joint hypermobility.[27] Some patients with HαT have an asymptomatic presentation. HαT may be diagnosed alone, but it is also enriched in patients with SM, especially ISM or SSM. It may also be found in patients with CM. HαT is associated with an increased risk of severe mediator symptoms and anaphylaxis.[28,29] While it is currently unclear how this symptom complex relates to increased copy number of the *TPSAB1* gene, testing for this inherited genetic variant may be considered. Since patients with SM can have symptoms of mast cell activation and also carry a diagnosis of HαT, it is important to apply WHO criteria to formally establish the diagnosis of SM.

Clinical Presentation

Mastocytosis is associated with a variety of symptoms related to the release of mast cell mediators and mast cell tissue infiltration.[30]

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.

While some patients present with isolated symptoms, others develop a constellation of symptoms related to mast cell activation. The most common clinical symptoms include cutaneous symptoms (eg, flushing of the face, neck, and chest; pruritus; itching; hives with or without angioedema; skin rashes), wheezing and shortness of breath, dizziness, syncope, cardiovascular symptoms (ie, rapid heart rate, chest pain, low blood pressure), gastrointestinal symptoms (eg, diarrhea, nausea, vomiting, abdominal pain, bloating, gastroesophageal reflux disease), fatigue, musculoskeletal symptoms (ie, bone/muscle pain), and neuropsychiatric symptoms (eg, headache and/or brain fog, cognitive dysfunction, anxiety and depression).[31-34]

Symptoms occur either spontaneously or in response to triggers of mast cell activation (eg, sunlight, heat, cold or sudden temperature changes, physical and emotional stress, food, alcohol consumption, insect stings, venoms, infections, drugs [ie, opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics (eg, vancomycin, quinolones), anesthetic agents], contrast dyes, surgery, other clinical procedures [eg, endoscopy, colonoscopy]).[31,34]

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.[34] In the WHO and ICC 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% mast cells on bone marrow biopsy and serum total tryptase level >200 ng/mL); 2) signs of dysplasia or myeloproliferation in non-mast cell lineage(s), but criteria are not met for the definitive diagnosis of an AHN, with normal or only slightly abnormal blood counts; and 3) for hepatomegaly without impairment of liver function, palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging.[2,12] In the ICC classification, instead of signs of dysplasia or myeloproliferation in non-mast cell lineage, B-finding is modified to “Cytopenia (not meeting criteria for C-findings) or -cytosis. Reactive causes are excluded, and criteria for other myeloid neoplasms are not met.”[12] In the WHO 5th edition classification, a *KIT* D816V variant allele frequency (VAF) greater than or equal to 10% is a qualifying B-finding.[13]

C-Findings

C-findings 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 one or more cytopenia(s) (eg, absolute neutrophil count [ANC] <1 x 10^9/L; hemoglobin level <10 g/dL; and/or platelet count <100 x 10^9/L due to bone marrow dysfunction by neoplastic mast cell infiltration); palpable splenomegaly with hypersplenism; skeletal involvement, with large osteolyses ($\geq$2 cm) with or without pathologic fractures; palpable hepatomegaly with impairment of liver function, and/or ascites, and/or portal hypertension; and malabsorption (eg, hypoalbuminemia) with weight loss due of gastrointestinal mast cell infiltrates.[2,33]

Diagnostic Criteria for Variants of Systemic Mastocytosis

Indolent Systemic Mastocytosis

ISM meets the general criteria for SM and is characterized by low mast cell burden, and no evidence of C-findings or an AHN.[2] Skin lesions are also frequently present. 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%).[17] Patients with ISM exhibit a life expectancy similar to that of an age-matched general population, with a median survival of 301 months. Using data from the registry of the European Competence Network on Mastocytosis (ECNM), which comprised 1639 patients with SM, Sperr et al[35] reported a median overall survival (OS) of 28.4 years (95% CI, 24.1–32.8 years) and a survival rate of 93.5% (95% CI, 90.1%–95.8%) at 10 years for patients with ISM. About 2.9% of patients will progress to advanced SM.[36]

Bone Marrow Mastocytosis

In the 2022 WHO classification, BMM is a separate category from ISM but in the ICC classification, it is a subvariant of ISM.[12,13] Diagnostic criteria are the same as ISM; however, mast cell infiltration is confined to the bone marrow with no skin or multiorgan visceral lesions.[2,17,37] 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).[17]

Smoldering Systemic Mastocytosis

SSM meets the general criteria for ISM.[2] It is defined by two or more B-findings, and no evidence of C-findings or an AHN. SSM is characterized by a relatively high mast cell burden, older age at presentation, and higher frequency of constitutional symptoms (45%).[17] 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). However, patients with SSM were significantly older; in a multivariate analysis, advanced age was the primary determinant of inferior 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] Registry data from the ECNM revealed that the median OS was not reached and the survival rate was 84.5% (95% CI, 61.1%–84.5%) at 10 years for patients with SSM.[35]

Aggressive Systemic Mastocytosis

The diagnosis of ASM requires meeting the general criteria for SM and the presence of one or more C-findings, but does not meet the criteria for 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 of SM-AHN, even if C-findings are felt to be related to the mast cell component. Skin lesions are usually absent and are less common in ASM compared to ISM. The median survival of patients with ASM was 41 months in one study.[16] ASM with 5% to 19% mast cells in a bone marrow aspirate is referred to as ASM in transformation.

Systemic Mastocytosis with an Associated Hematologic (Myeloid) Neoplasm

SM-AHN meets the general criteria for SM as well as the diagnostic criteria for the AHN.[2] In KIT inhibitor trials of patients with advanced SM, SM-AHN has comprised approximately 70% of enrolled patients.[38-40] C-findings may or may not be present. AHNs are of myeloid lineage in the overwhelming majority of patients (~90%) and lymphoid neoplasms (eg,

chronic lymphocytic leukemia [CLL], lymphomas, multiple myeloma) are uncommon.[41,42] In addition, lymphoid neoplasms are generally not considered related to the SM clone. AHNs of myeloid lineage include AML, MPN, myelodysplastic syndromes (MDS), MDS/MPN (eg, chronic myelomonocytic leukemia [CMML] or MDS/MPN-unclassifiable [MPN-U]), and chronic eosinophilic leukemia, not otherwise specified (CEL, NOS).[41,42] MDS/MPNs (eg, CMML) are the most common type of AHN found in SM-AHN.

SM-AHN is characterized by older age at presentation, higher incidences of constitutional symptoms and hematologic abnormalities, and an inferior OS compared with other subtypes of SM without AHN.[43] The outcome of patients with SM-AHN varies with the type of AHN. One study found that SM-MDS and SM-MPN were associated with significantly longer median survival (42 months and 32 months, respectively) compared to SM-CMML (17 months), SM-MDS/ MPN-U (16 months), and SM-AML (11 months).[42] The rate of leukemic transformation was more frequent in SM-MDS (29%) than in SM-MPN (11%) or SM-CMML (6%).[41]

Mast Cell Leukemia

MCL is defined histopathologically by the presence of greater than or equal to 20% neoplastic mast cells on a bone marrow aspirate smear.[2] The ICC does not distinguish between acute and chronic MCL (see below) and only uses the term MCL.[12] In addition, in cases where an aspirate is a dry tap and unevaluable, MCL may be diagnosed on a core biopsy if a dense, diffuse infiltrate of atypical, immature mast cells is present.

The aleukemic variant (<10% circulating mast cells in peripheral blood) is much 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.[44-46]

MCL can present as a *de novo* disorder, or it can transform from advanced forms of SM such as ASM, SM-AHN or, very rarely, ISM.[16,47,48] 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, morphologic, or molecular characteristics between the two variants.[48] AHNs (CMML, CEL, MDS, and MDS/MPN-U) were diagnosed in 71% of patients with MCL (20 out of 28) and is generally associated with a worse prognosis, even within the spectrum of MCL. *KIT* D816V mutation was identified in 68% of patients and additional prognostically relevant mutations in *SRSF2/ASXL1/ RUNX1* (*S/A/R*) genes, considered high-risk mutations, were identified in 52% of patients. In another study, the ECNM registry evaluated patients with MCL.[49] An AHN was found in 34% of patients and 14% of patients had chronic MCL. *KIT* D816V mutations, *S/A/R* mutations, and an abnormal karyotype were identified in 73%, 44%, and 17% of patients, respectively. A median OS of 1.6 years was reported. A diagnosis of MCL-AHN, an abnormal karyotype, and the absence of *KIT* D816V were associated with reduced OS.

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 biopsy-proven adult-onset mastocytosis in the skin (MIS).

Initial evaluation should include a physical examination, skin examination for cutaneous lesions, palpation of spleen and liver, history of anaphylaxis, mast cell activation symptoms, potential triggers, and documentation of medications/transfusion history and weight loss. Laboratory evaluation should include comprehensive metabolic panel with uric acid, lactate dehydrogenase, liver function tests, complete blood count (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 if biopsy of that organ is felt to be important for clinical management or to ascertain whether mast cell involvement is the basis for organ damage; high-sensitivity mutation analysis for the detection of *KIT* D816V mutation and multigene next-generation sequencing (NGS) panel that includes genes such as *SRSF2*, *ASXL1*, and *RUNX1*; mast cell immunophenotyping by immunohistochemistry (IHC) and/or flow cytometry; imaging studies to document organomegaly, lymphadenopathy, and/or ascites (eg, B- and/or C-findings); and human leukocyte antigen (HLA) testing, if considering allogeneic hematopoietic cell transplantation (HCT) as a future option. Twenty-four-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 in *24-Hour Urine Studies*.

Serum Tryptase Level

Serum tryptase is elevated in the vast majority of patients with SM across all subtypes.[50] However, a minority of patients with SM have a tryptase level below the minor diagnostic criterion level of 20 mg/mL, or more rarely in normal range, due to a very low neoplastic mast cell burden.[51] Elevated levels of serum tryptase have also been documented in patients with other myeloid malignancies, MCAS, HαT, and renal failure.[27,52,53] Therefore, 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.[54]

Serum total tryptase (>20 ng/mL) is one of the minor criteria unless an AMN is present.[12,14] 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, and the co-occurrence of HαT, which may also contribute to elevation of the serum tryptase level.[27,52,53] Bone marrow evaluation should be done to confirm the diagnosis of SM in patients who are symptomatic with persistently elevated levels of serum tryptase.[53]

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.[2] 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.

Bone marrow aspiration and biopsy with mast cell immunophenotyping is almost always necessary to establish the diagnosis of SM.[55] 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.[56]

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 (H&E) staining.[57,58] The expression of CD2, CD25, and/or CD30 expression on mast cells is a minor diagnostic criterion.[12,14]

Neither tryptase nor CD117 immunostaining is able to distinguish between normal and neoplastic mast cells.[59-61] Aberrant expression of CD2 and CD25 are useful to differentiate mast cells in SM from normal/reactive mast cells in the bone marrow.[61-63] 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 patients with ISM.[60,64,65] 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.[66]

Cytoplasmic and/or surface expression of CD30 has also been reported in neoplastic mast cells in patients with SM and is now added as a minor criterion for the diagnosis of SM.[12,13,18,22,67-69] Earlier reports suggested that CD30 is preferentially expressed in the neoplastic mast cells of advanced SM compared to ISM.[67,68] However, some reports confirmed 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.[22,69] However, an 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.[18,22]

IHC with markers for mast cell tryptase, CD117, CD25, and CD30 should be performed for the quantification of mast cell burden in bone marrow.[59-63] CD34 staining may also be obtained to quantify whether the proportion of myeloblasts is increased, especially in SM-AHN.[70] Flow cytometry is a complementary tool for the diagnosis or monitoring of SM. CD117, CD25, CD30, and CD2 are the standard markers.[71,72]

Molecular Testing

KIT D816V mutation occurs in the majority of patients (>90%) with SM.[7,41,73,74] 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 the 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%).[75]

In addition to *KIT* D816V mutation, prognostically relevant mutations in several other genes (*TET2, SRSF2, CBL, ASXL1, RUNX1, EZH2, JAK2,* and/or *RAS)* have also been identified in advanced SM.[76-84] The presence of one or more mutations beyond *KIT* D816V, particularly in the *SRSF2, ASXL1, RUNX1* (*S/A/R*), and/or *EZH2* genes, has been associated with significantly inferior OS and progression-free survival (PFS).[78,80,81,83,84] In addition, the presence of mutations in the *ASXL1, RUNX1,* and/or *DNMT3A* genes with VAFs greater than or equal to 30% has also been identified as an independent predictor for PFS in ISM.[85]

More refined prognostic scoring systems integrating clinical variables and high-molecular-risk (HMR) mutations have been developed for the risk stratification of patients with SM (See *Risk Stratification*).[35,86,87] 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.

Eosinophilia is more prevalent in patients with advanced SM and is a predictor of inferior survival outcomes.[88,89] 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.[90,91] Atypical or spindle-shaped mast cells that also express CD25 may be found in the bone marrow of such patients, usually in a loosely scattered or interstitial pattern without forming multifocal aggregates.[92] 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 *FIP1L1::PDGFRA* fusion in patients with eosinophilia is critical since it is a predictor of excellent response to imatinib.[93,94] The *FIP1L1::PDGFRA* fusion oncogene should be tested in peripheral blood in patients with eosinophilia who do not have the *KIT* D816V mutation.

KIT D816V Mutational Analysis

Detection of the *KIT* D816V mutation (or another activating mutation in the *KIT* gene) in the bone marrow, blood, or another extracutaneous organ is included as a minor criterion.[12,13] Myeloid mutation panels alone are not recommended for the detection of *KIT* D816V since NGS assays can exhibit low sensitivity and higher-sensitivity assays should always be performed.

Mutation analysis for *KIT* D816V is preferably done using a 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 (DHPLC), peptide nucleic acid (PNA)-mediated PCR, allele-specific oligonucleotide quantitative reverse transcriptase polymerase chain reaction (ASO-qPCR),[95] and digital droplet PCR.[96] In the absence of a highly sensitive quantitative PCR assay, qualitative PCR can be used.

ASO-qPCR is a highly sensitive method for the detection of *KIT* D816V mutation in various tissues.[97] Several studies have reported the possibility of detecting the *KIT* D816V in peripheral blood using a highly sensitive ASO-qPCR or digital droplet PCR.[96,98-100] 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 for *KIT* D816V with a highly sensitive ASO-qPCR or digital droplet PCR assay can first be 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 less than 20 ng/mL, and those who lack multifocal mast cell clusters in a bone marrow biopsy.[57,58]

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.[95] In patients with a high mast cell burden who are otherwise negative for *KIT* D816V mutation, molecular testing should be confirmed with ASO-qPCR or digital droplet PCR, 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.[101] 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 Competence Network on Mastocytosis (IWG-MRT-ECNM) and the modified IWG-MRT-ECNM (mIWG-MRT-ECNM) criteria are used to establish eligible organ damage

findings for enrollment of patients into clinical trials and to adjudicate response to therapy.[102,103] The proposed ECNM-American Initiative in Mast Cell Diseases (ECNM-AIM) criteria use tiered response criteria that separate SM (and AHN) pathologic response, *KIT* molecular response, clinical (organ damage) response, and symptom/quality-of-life [QOL] response in the setting of clinical trials (see *Response Criteria*).[104] 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.[2,102]

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 IHC (CD117, CD25, tryptase, and CD3 as a control T-cell marker).

Osteoporosis and osteopenia are the most common bone complications in patients with SM; the risk of osteoporosis and vertebral fractures is high in patients with ISM, and higher urinary N-methylhistamine levels are also associated with a higher risk of osteoporosis.[33,105-109] In advanced SM, the finding of an increased bone mineral density (BMD) compared to those without elevated BMD was associated with a more aggressive phenotype and inferior survival.[109]

Skeletal involvement, with large (≥2 cm) osteolytic lesions with or without pathologic fractures is considered a C-finding. However, the presence of one or more small osteolytic and/or sclerotic 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 consideration of a metastatic skeletal survey to evaluate for osteolytic lesions (in patients with clinical suspicion of focal disease) are recommended as part of the initial workup for ISM and SSM. Whole body MRI to evaluate for the presence of osteolytic lesions is still a research-based imaging modality.[110]

24-Hour Urine Studies

The measurement of urinary metabolites of histamine and prostaglandin in a 24-hour urine sample or spot urine has been shown to correlate with mast cell burden and activation.[111] N-methylhistamine, prostaglandin D2, and 2,3-dinor-11 beta-prostaglandin F2 alfa are the most commonly measured metabolites.[112-117] Any elevation above normal is considered significant; however, cut-off levels for significant elevation of these metabolites have not been established.

While such 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).[107,118]

Risk Stratification

The Mayo Alliance Prognostic System (MAPS) and Mutation-Adjusted Risk Score (MARS) use a combination of clinical variables and HMR mutations for risk stratification.[86,87] However, since HMR mutations were not seen in patients with ISM and SSM, both MAPS and MARS are primarily applicable only for patients with advanced SM. International

Prognostic Scoring System for Mastocytosis (IPSM) score is based only on the clinical variables and is useful for the risk stratification of patients with ISM/SSM and advanced SM.[35] The Global Prognostic Score for Mastocytosis (GPSM) is based on clinical variables that are prognostic factors for OS and PFS.[119]

MAPS

In a study of 580 patients with SM (ISM/SSM, n = 291; SM-AHN, n = 199; ASM, n = 85; and MCL, n = 5), clinical variables including age >60 years, advanced SM (vs. ISM/SSM), thrombocytopenia (platelets <150 x 10^9/L), anemia (hemoglobin level below sex-adjusted normal), and increased alkaline phosphatase (ALP) were identified as independent risk factors for survival.[86] In addition, the presence of *ASXL1, RUNX1,* and *NRAS* mutations were independently associated with inferior survival. In the combined clinical and molecular risk factor analysis, the presence of HMR mutations, advanced SM, thrombocytopenia, increased ALP, and age >60 years retained prognostic significance. Patients with SM are stratified into four different risk groups (low, intermediate-1, intermediate-2, and high) with significantly different median survival (not reached, 85 months, 36 months, and 12 months, respectively). This risk stratification is applicable only for patients with advanced SM.

MARS

In a study that included 231 patients with advanced SM in the training cohort (ASM, n = 30; SM-AHN, n = 181; and MCL, n = 20), age >60 years, hemoglobin less than 10 g/dL, platelets less than 100 x 10^9, the presence of one HMR mutation (*SRSF2, ASXL1*, and/or *RUNX1* [*S/A/R*]), and the presence of two or more *S/A/R* mutations were independent predictors of inferior OS.[87] The presence and number of *S/A/R* mutations had a significant prognostic impact on OS. The weighted score was developed by assigning 2 points for the presence of two or more *S/A/R* mutations and 1 point for each of the other adverse factors. Patients with advanced SM were stratified into three risk groups (low, intermediate, and high). The median OS was not reached for the low-risk group compared to 4 years and 2 years, respectively, for the intermediate and high-risk groups.

IPSM

In a large cohort of patients with mastocytosis (n = 1639; ISM, n = 1006; SSM, n = 53; SM-AHN, n = 174; ASM, n = 62; and MCL, n = 23), age ≥60 years, and ALP greater than 100 u/L were identified as predictors of higher-grade mastocytosis and OS in patients with non-advanced mastocytosis (CM, MIS, ISM, and SSM).[35] Age ≥60 years, tryptase greater than or equal to 125 ng/mL, leukocytes greater than or equal to 16 x 10^9/L, hemoglobin less than or equal to 11 g/dL, platelets less than or equal to 100 x 10^9/L, and skin involvement were independent prognostic factors for OS in patients with advanced SM. IPSM was validated in a cohort of 462 patients (ISM, n = 384; SSM, n = 11; advanced SM, n = 49).

Patients with non-advanced SM were stratified into three risk groups (low, intermediate-risk 1 [INT-1], and intermediate-risk 2 [INT-2]) with significantly different OS (10-year OS rates were 87%, 52%, and 22%, respectively) and PFS (10-year PFS rates were 96%, 87%, and 76%, respectively). The difference in OS and PFS was significant among the three risk groups for patients with ISM, whereas the OS rates were not significant between the risk groups for patients with SSM.

Patients with advanced SM were stratified into four risk groups (advanced SM 1 [AdvSM-1], advanced SM 2 [AdvSM-2], advanced SM 3 [AdvSM-3], and advanced SM 4 [AdvSM-4]). The OS for patients in risk groups AdvSM-1 and AdvSM-2 was similar to that of patients with non-advanced mastocytosis in the INT-1 and INT-2 risk groups, respectively.

GPSM

Prognostic parameters were examined in a discovery cohort of 422 patients with SM (ISM, n = 368; SSM, n = 4; ASM, n = 18; SM-AHN, n =

31; and MCL, n = 1).[119] The clinical variables that were prognostic for PFS were platelet count less than or equal to 100 x 10^9/L, serum β2-microglobulin greater than or equal to 2.5 µg/mL, and serum baseline tryptase greater than or equal to 125 µg/L. The clinical variables that were prognostic for OS were hemoglobin less than or equal to 11 g/dL, serum ALP greater than or equal to 140 IU/L, and presence of *SRSF2*, *ASXL1*, *RUNX1*, or *DNMT3A* gene mutations. Using the GPSM-PFS (n = 399) and GPSM-OS (n = 411) models, patients were stratified into three risk groups (low-risk, intermediate-risk, and high-risk). The PFS at 5 years was 100%, 94%, and 47%, respectively, while the OS at 5 years was 100%, 94%, and 62%, respectively. These results were corroborated in a validation cohort of 853 patients (ISM, n = 607; SSM, n = 19; ASM, n = 44; SM-AHN, n = 171; and MCL, n = 12). After patient stratification in the low-, intermediate-, and high-risk groups using GPSM-PFS (n = 670) and GPSM-OS (n = 768) models, the 5-year PFS was 98%, 84%, and 43%, and the 5-year OS was 99%, 61%, and 30%, respectively.

A comparison of different scoring models showed that the GPSM-PFS model had a high prognostic capability, especially in patients with non-advanced SM.[119] For patients with advanced SM, the GPSM-OS model and the IPSM model for advanced SM were the best predictive models.

Treatment Recommendations

Referral to specialized centers with expertise in the management of mastocytosis is strongly recommended.[4-6] Multidisciplinary collaboration with subspecialists (eg, allergists for the management of anaphylaxis and drug hypersensitivities, anesthesiologists for invasive procedures or surgery; high-risk obstetrician for pregnancy) is recommended.

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.[34]

Anti-mediator drug therapy for mast cell activation symptoms (as described below) is recommended for all patients with SM. Patients should be counseled about the signs and symptoms of mast cell activation[120] 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-I.[120] The advanced SM symptom assessment form (AdvSM-SAF) is a 10-item patient-reported outcome instrument that assesses the severity of the following symptoms: abdominal pain, nausea, vomiting, diarrhea, spots, itching, flushing, and fatigue.[120] The frequency of vomiting and diarrhea are also taken into account. Anaphylactic reactions are significantly more frequent in patients with ISM and should be managed with the use of epinephrine injection. All patients should carry two 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 radiologic procedures can induce mast cell activation and anaphylaxis.

Potential cytoreductive options for advanced SM include avapritinib, midostaurin, cladribine, or peginterferon alfa-2a. Peginterferon alfa-2a is an option for ASM and SM-AHN (when the SM component requires prioritization over the AHN component) but is not recommended for MCL with or without an AHN. However, cladribine or peginterferon alfa-2a may also be useful in select patients with symptomatic 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. Given the potential toxicities associated with cladribine therapy, including drug-related myelosuppression and infections, the risks and potential benefits of such treatment need to be weighed in this non-advanced SM population.

In patients with SM-AHN, an initial assessment is undertaken to determine whether the SM component or the AHN component requires prioritization.

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 (eg, 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,[44-46] cytoreductive therapy should still be considered for such patients given the poor prognosis of both MCL subtypes.

Enrollment in well-designed clinical trials investigating state-of-the-art therapeutic strategies (eg, highly 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 the algorithm on SM-K.[121] 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, vomiting); neurological symptoms (eg, headache, poor concentration and memory, brain fog); cardiovascular symptoms (eg, pre-syncope, syncope, tachycardia); pulmonary symptoms (eg, wheezing, throat swelling); and naso-ocular symptoms (eg, nasal stuffiness or pruritus, conjunctival injection).[122]

Cromolyn sodium is effective for the management of cutaneous, gastrointestinal, and neurological symptoms.[123-126] In one double-blind crossover 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.[123] In another double-blind crossover 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.[124] Topical cromolyn sodium (emulsion, ointment, or cream; 1%–4%) is effective for the symptomatic relief of pruritus, itch, and flare caused by intradermal histamine and can be used to decrease flare-ups of cutaneous symptoms in response to triggers.[125,126]

Aspirin, corticosteroids, and leukotriene receptor antagonists are useful for the management of symptoms that are refractory to other treatment options.[122] In particular, leukotriene receptor antagonists have been used for the management of skin and gastrointestinal symptoms that have not responded to other therapies.[127,128] Aspirin has been shown to be effective for the management of symptoms associated with elevated urinary prostaglandin levels.[129] However, the risks and benefits of aspirin need to be weighed carefully since it can trigger mast cell activation in some patients.

Omalizumab, an anti-immunoglobulin E (IgE) monoclonal antibody, has been shown to be effective for symptoms related to mast cell mediator release in patients with mastocytosis.[130-137] In a systematic review that assessed the efficacy and safety of omalizumab for the treatment of symptoms related to mast cell mediator release in adult patients with mastocytosis, omalizumab was particularly effective for recurrent anaphylaxis, skin, and gastrointestinal symptoms as opposed to for neuropsychiatric, respiratory, and musculoskeletal symptoms.[138]

Omalizumab can be used for the management of symptoms related to mast cell mediator release, insufficiently controlled by conventional therapy.

Management of Anaphylaxis

The prevalence of anaphylaxis has been reported in 24% to 49% of patients with SM.[31,139,140] Increased serum tryptase levels have been identified as a risk factor for anaphylaxis in some studies,[31,141] 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.[141-143]

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.[144,145] Hymenoptera venom allergy is an established risk factor for severe recurrent anaphylaxis in patients with SM.[146] Hymenoptera venom anaphylaxis is more prevalent in patients with ISM and it seems to be absent in patients with advanced SM with high mast cell burden.[147] 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.[148-151] 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.[150] *KIT* D816V mutation has been implicated in the hyperactivity of mast cells by amplifying the IgE-dependent mast cell mediator release.[152] 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. First-generation anticholinergic antihistamines are not recommended in adult patients >65 years of age.[153] Epinephrine injection is the preferred treatment for systemic hives with organ involvement (ie, 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.[145]

Venom immunotherapy (VIT) is effective for the treatment of IgE-mediated Hymenoptera venom anaphylaxis in patients with SM and has also been shown to significantly reduce the risk of anaphylaxis after a re-sting.[154-157] 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.[145]

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.[130-132] Omalizumab can also improve tolerance while on VIT.

Management of Osteoporosis

Supplemental calcium and vitamin D are recommended.[158,159] The use of bisphosphonates (with continued use of antihistamines) is recommended to resolve bone pain and improve vertebral BMD.[160] 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.[161,162] Peginterferon alfa-2a may be considered for patients with refractory bone pain and/or worsening BMD on bisphosphonate therapy.[163-165]

Denosumab, an anti-RANKL monoclonal antibody, has also been associated with significant increases in BMD at lumbar and femoral sites, and decreases in bone turnover markers in serum (mainly C-terminal telopeptide of collagen type I and bone ALP to a lesser extent).[166] Denosumab can be used as a second-line therapy for patients with bone pain not responding to bisphosphonates or for patients who are not candidates for bisphosphonates because of renal insufficiency. A U.S. Food and Drug Administration (FDA)-approved biosimilar is an appropriate substitute. Vertebroplasty or kyphoplasty could also be performed in selected patients for refractory pain associated with vertebral compression fractures.[167]

Cytoreductive Therapy

In the NCCN Guidelines, regimens for cytoreductive therapy are stratified into three categories (based on the evidence, efficacy, toxicity, and in some cases access to certain agents): preferred regimens, other recommended regimens, and useful in certain circumstances.

The management of mast cell activation symptoms with anti-mediator drug therapy is recommended for symptomatic ISM or SSM. Enrollment in a clinical trial is a preferred option for these patients. Avapritinib (if platelet counts are ≥50 x 10^9/L)[168] is also a preferred option for patients with symptomatic ISM. Additionally, for symptomatic ISM or SSM, cladribine[169-171] or peginterferon alfa-2a[172-175] may be useful in certain circumstances for select patients with severe, refractory mediator symptoms or bone disease not responsive to anti-mediator therapy or bisphosphonates.[121]

Enrollment in a clinical trial, avapritinib (if platelet counts are ≥50 x 10^9/L),[39,40] and midostaurin[38,176,177] are preferred regimens and cladribine[169-171] and peginterferon alfa-2a (± prednisone)[172-175] are other recommended regimens for patients with ASM, SM-AHN (when the SM component requires prioritization over the AHN component), and MCL (with or without an AHN) (except for peginterferon alfa-2a ± prednisone). Imatinib is included as a useful in certain circumstances treatment option for the rare patients with ASM (for *KIT* D816V mutation negative after testing with a high-sensitivity assay or unknown, WDSM, or if eosinophilia is present with *FIP1L1::PDGFRA* gene fusion, which operationally redefines the patients as having a myeloid/lymphoid neoplasm with eosinophilia and tyrosine kinase gene fusions as defined by the WHO and ICC).[21,178-184]

Avapritinib

Avapritinib, a potent and selective inhibitor of *KIT* D816V, has demonstrated activity in patients with ISM and advanced SM[40,168] and is FDA-approved for the treatment of adult patients with ISM and advanced SM, including ASM, SM-AHN, and MCL.

Indolent SM

In the phase II PIONEER trial, patients with moderate to severe ISM despite prior use of 2 or more best supportive care medications were randomized 2:1 to receive avapritinib (25 mg daily) or placebo.[168] At 24 weeks, a reduction of 15.6 points (95% CI, -18.6 to -12.6) from baseline in the total symptom score was reported in patients treated with avapritinib compared to a reduction of 9.2 points (95% CI, -13.1 to -5.2; P = .003) in those treated with placebo. Compared to patients treated with placebo, those treated with avapritinib also achieved a 50% or greater decrease in serum tryptase level (54% vs. 0%; P < .001), *KIT* D816V VAF in peripheral blood (68% vs. 6%; P < .001), total symptom score (25% vs. 10%; P = .005), and bone marrow mast cell burden (53% vs. 23%; P < .001). Grade 3 or higher adverse events occurred at similar rates in both groups. The most common adverse events that occurred in the avapritinib group at a rate of two times or more than that of the placebo group included flushing (9.2% vs. 4.2%), peripheral edema (8.5% vs. 4.2%), face edema (7.1% vs.

1.4%), elevated blood ALP (6.4% vs. 1.4%), periorbital edema (6.4% vs. 2.8%), and insomnia (5.7 vs. 2.8%). The number of anaphylactic events in both groups were low and the trial was not powered to determine a difference in the frequency of anaphylaxis between the two groups.

Advanced SM

Data from the phase I EXPLORER trial, which consisted of 53 evaluable patients with advanced SM (ASM, n = 3; SM-AHN, n = 37; MCL, n = 13) treated with a dose of 30 to 400 mg once daily (dose escalation and expansion stages), revealed an overall response rate (ORR) of 75% (95% CI, 62%–86%) (100% [95% CI, 29%–100%] for ASM, 76% [95% CI, 59%–88%] for SM-AHN, and 69% [95% CI, 39%–91%] for MCL), per the mIWG-MRT-ECNM response criteria.[39] Ninety-two percent, 80%, and 99% of patients reported a 50% or greater decrease from baseline in bone marrow mast cells, *KIT* D816V variant allele fraction, and serum tryptase, respectively. A decrease of 35% or greater in spleen volume from baseline was obtained in 82% of patients. Across all patients (n = 86), the most common grade 3 and above non-hematologic adverse events were fatigue (9%) and vomiting (5%) while the most common grade 3 and above nonhematologic adverse events were thrombocytopenia (34%), anemia (30%), and neutropenia (15%). There were nine cases of intracranial bleeding (ICB) in patients with advanced SM (13% of 69 patients in the advanced SM safety population), seven of which were associated with antecedent severe thrombocytopenia.

A pre-specified interim analysis of the phase II PATHFINDER trial, which comprised 32 evaluable patients with advanced SM (ASM, n = 2; SM-AHN, n = 26; MCL, n = 4) treated with avapritinib at a starting dose of 200 mg once daily, reported an ORR of 75% (95% CI, 57%–89%), as assessed by the mIWG-MRT-ECNM response criteria.[40] The ORR was 100% (95% CI, 16%–100%), 81% (95% CI, 61%–93%), and 25% (1%–81%) in patients with ASM, SM-AHN, and MCL, respectively. The safety population (n = 62) was used to assess secondary endpoints. Patients experienced reductions in objective measures of mast cell disease burden. The percentages of patients who achieved a 50% or greater decrease from baseline in bone marrow mast cells, *KIT* D816V variant allele fraction, and serum tryptase were 88%, 60%, and 93%, respectively. A decrease of 35% or greater in spleen volume from baseline was obtained in 66% of patients. An amelioration in patient-reported symptoms, as assessed by the AdvSM-SAF total symptom score, was also reported (P < .001). The most common grade 3 or above hematologic adverse events were neutropenia, thrombocytopenia, and anemia, and occurred in 24%, 16%, and 16% of patients, respectively. The most common grade 3 or above nonhematologic adverse events were increased blood ALP (5%), peripheral edema (3%), periorbital edema (3%), and fatigue (3%). The study reported one instance (1.6%) of ICB in a patient with severe thrombocytopenia at baseline. As patients with severe thrombocytopenia at baseline had an increased risk of ICB, the study protocols for both the EXPLORER and PATHFINDER trials were amended to exclude patients with platelet counts <50 x 10^9/L as part of the mitigation strategies to reduce ICB.[39,40]

Comparison between avapritinib and best available therapy was performed in one retrospective study that pooled data from a multi-center study whereby patients with advanced SM were treated with best available therapy and data from the EXPLORER and PATHFINDER trials.[185] Median OS was significantly improved in patients treated with avapritinib (49.0 months [95% CI, 46.9 months–not estimable] vs. 26.8 months [95% CI, 18.2–39.7 months]; adjusted hazard ratio [HR], 0.48; 95% CI, 0.29–0.79; P = .004). Data further demonstrated that avapritinib treatment was associated with improved OS compared to midostaurin (HR, 0.59; 95% CI, 0.36–0.97; P < .001) and cladribine (HR, 0.32; 95% CI, 0.15–0.67; P = .003).[186] OS was also improved in patients with SM-AHN treated with avapritinib compared to best available therapy.[187] The duration of

treatment (HR, 0.36; 95% CI, 0.26–0.51; *P* < .001) and the maximum decrease in serum tryptase level (mean difference of -60.3%; 95% CI, -72.8% to -47.9%; *P* < .001) were significantly higher in patients with advanced SM treated with avapritinib.[185] The efficacy of avapritinib in patients with advanced SM was established irrespective of prior therapies or *S/A/R* mutation status.[188]

Midostaurin

Midostaurin, an oral multikinase inhibitor with activity against D816V-mutated *KIT*, has demonstrated activity for the treatment of advanced SM[38,176,177] and is FDA-approved only for patients with a diagnosis of ASM, SM-AHN, or MCL, although it has also been shown to be effective for patients with ISM and severe symptoms related to mast cell mediator release or skin infiltration in a small phase II clinical trial.[189]

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. Using modified Valent and Cheson response criteria, treatment with midostaurin (100 mg twice daily) resulted in an 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).[38] 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 had unknown mutation status), or exposure to previous therapy. The median OS and 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 greater than or equal to 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 patients, respectively, and were more common in patients with pre-existing cytopenias.

A 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 OS were significantly higher in patients with an $S/A/R^{neg}$ (vs. $S/A/R^{pos}$) mutation profile and in patients with a greater than or equal to 25% (vs. <25%) reduction in the RNA expressed allele burden.[190] The acquisition of additional mutations in *KRAS, NRAS*, *RUNX1*, *IDH2*, or *NPM1* genes was identified in patients with disease progression. Another study reported an amelioration in the mast cell mediator-related symptoms in patients with advanced SM who were treated with midostaurin.[191]

Cladribine

Cladribine (2-chlorodeoxyadenosine) is not approved by the FDA for SM, but is used on an off-label basis because of its activity across all subtypes of SM, including MCL refractory to prior cytoreductive therapy.[169-171] Cladribine may be particularly useful for patients with advanced SM when rapid debulking of disease is required.

In an analysis, treatment with cladribine resulted in an ORR of 56%, 50%, and 55%, in patients with ISM, ASM, and SM-AHN, respectively.[170] The presence of circulating immature myeloid cells was a predictor of inferior response. In a 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%).[171] The median duration of response was 4 years and 3 years for ISM and ASM, respectively. 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.

Peginterferon alfa-2a with or without prednisone

Interferon alfa (with or without prednisone) carries the potential to induce a 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, across all subtypes of SM.[172-175] However, because of their cytostatic mechanism of action, responses may take longer to emerge, and the use of interferons may be more suitable for patients with slowly progressive disease (PD) without the need for rapid cytoreduction. In the current era of KIT inhibitors, the therapeutic value of interferon therapy is less clear.

Imatinib

Imatinib is FDA-approved for the treatment of adult patients with ASM without the *KIT* D816V mutation or with unknown *KIT* mutational status and is very effective in the treatment of patients with eosinophilia-associated myeloid neoplasms characterized by the *FIP1L1::PDGFRA* gene fusion.[93,94] It has also 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.[21,178-184] 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 (CR) in four patients and partial response (PR) in one patient with wild-type *KIT*.[21]

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.[192-195] Data from transplant series are largely derived from the pre-KIT inhibitor era. Reduced-intensity conditioning regimens were associated with lower survival than myeloablative conditioning regimens. 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 a 70% response rate (28% CR; 21% stable disease [SD]) and the 3-year OS rate was 57% for all patients (74%, 43%, and 17% for patients with SM-AHN, ASM, and MCL, respectively).[194] MCL subtype was the strongest risk factor for poor OS. The role of allogeneic HCT needs to be determined in a prospective trial. In 2024, best practice recommendations were published for allogeneic HCT in patients with advanced SM.[195]

Evaluation for allogeneic HCT is a consideration for patients with advanced SM after adequate response to prior treatment. For patients with advanced SM with inadequate response or loss response to prior treatment, second-line therapy and allogeneic HCT should be considered after re-staging. Among patients with SM-AHN, allogeneic HCT should also be considered as part of initial treatment when the AHN component requires HCT or if the AHN component progresses. Prophylactic anti-mediator drug therapy (corticosteroids, antihistamines, anti-IgE antibody, and epinephrine) should be used as needed with the conditioning regimen.[196] The role of KIT inhibitors in the post-transplant setting to minimize relapse has not been formally studied.

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.[102,197] These IWG-MRT-ECNM response criteria were developed mainly for use in clinical trials. The IWG-MRT-ECNM response criteria were subsequently modified, eg, mIWG-MRT-ECNM and are currently being used in trials of KIT inhibitors in advanced SM.[103] Treatment response criteria have also been published to adjudicate responses in the AHN component.

The revised 2013 IWG-MRT-ECNM response criteria delineated definitions for nonhematologic and hematologic organ damage eligible for response evaluation and adjudication of response.[102] 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 greater than or equal to one finding of nonhematologic or hematologic organ damage without concomitant worsening of other eligible organ damage.[102] CR and PR are defined based on the percent reduction in bone marrow mast cells and the reduction of serum tryptase levels.[102] In addition, the achievement of a CR or PR also requires the resolution of all or at least one CI finding, 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 PD, SD, and loss of response.

The mIWG-MRT-ECNM criteria allow splenomegaly of greater than or equal to 5 cm to be considered an eligible organ damage finding (“C-finding”) compared to the original IWG-MRT-ECNM criteria, which only allow symptomatic splenomegaly greater than 5 cm to be considered an organ damage finding.[102-104] The other significant change is that a response definition of complete remission with partial hematologic recovery (CRh) is now included, which is defined as a CR with the following counts: ANC ≥0.5 x 10^9/L, Hb ≥8.0 g/dL, and platelet count ≥50 x 10^9/L. The CRh category recognizes that in the absence of evidence of SM due to successful treatment, persistently low blood counts may instead relate to treatment-associated myelosuppression or the presence of an AHN.

More recently, consensus ECNM-AIM response criteria for advanced SM have been developed.[104] They include tiers of response to adjudicate different aspects of the disease: Tier IA is SM pathologic response and is adjudicated by evaluating bone marrow mast cell burden, serum tryptase level, and CBC results (eg, CR or CRh allowed); in the context of clinical trials, tier IA response serves as the primary endpoint. Tier IB is AHN pathologic response; tier II is molecular response evaluating changes from baseline in *KIT* D816V. Cytogenetic response, if abormal at baseline, is also included in Tier II response; Tier III is clinical response (based on mIWG-MRT-ECNM clinical improvement criteria), and Tier IV is symptom/QOL response. Tier IB through Tier IV are considered secondary endpoints in the setting of clinical trials.The major aim of these response criteria was to de-couple SM pathologic response from clinical response (Tier III) since unresolved C-findings can inappropriately downgrade an otherwise complete histopathologic response (eg, CR or PR to SD), which may underestimate clinical

benefit. In such cases, unresolved C-findings may reflect persistence of the AHN or other comorbidities, or may reflect organ damage that is slow to reverse (or irreversible).

Monitoring Response and Additional Therapy

ISM or SSM

History and physical examination, laboratory evaluation (annually for patients with ISM and every 6–12 months for patients with SSM), baseline DEXA scan (with serial evaluation based on severity and extent of bony disease 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.[15] Progressively increasing serum tryptase levels have been associated with disease progression to SSM or ASM and shorter PFS in patients with ISM.[198] Patients with ISM and SSM should also be monitored for the development of signs of disease progression to advanced SM (eg, development of 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).[102] 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.[102] 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.[102] Additional staging studies include CBC for the evaluation of hematologic organ damage, liver functions tests (measurement of total bilirubin, alanine aminotransferase, aspartate aminotransferase, and serum ALP [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 examination 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. While incorporated into current clinical trials of KIT inhibitors, the role of *KIT* D816V allele burden monitoring during treatment has not been formally established in clinical practice.[199,200]

Additional Therapy

The panel acknowledges that response criteria were developed mainly for use in clinical trials and that clinical benefit may not reach the threshold of these response criteria.[102-104] Response assessment should be based on the improvement of symptoms related to mast cell mediator release 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 (symptomatic ISM or SSM) or cytoreductive therapy (advanced SM). Evaluation of allogeneic HCT should be considered an option for patients with advanced SM (ASM, SM-AHN when the SM component requires prioritization over the AHN component, or MCL with or without an AHN) with suitable performance

status and if with adequate response to cytoreductive therapy and with suitable donor(s) are identified.[194,196]

Patients with ISM or SSM with inadequate response or loss of response or progression to advanced SM should be treated with cytoreductive therapy. Re-staging (as described above) is recommended for patients with advanced SM with inadequate response or loss of response. Second-line therapy and allogeneic HCT should be considered. Clinical trials are always recommended for these orphan diseases, regardless of whether patients have ISM, SSM, or advanced forms of SM.

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.[201] 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 symptoms related to mast cell mediator release (such as temperature extremes [hypothermia or hyperthermia] and unnecessary trauma) are strongly recommended.[202]

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.[203] Nevertheless, the use of perioperative drugs is not contraindicated in patients with SM.[202,204] 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 symptoms related to mast cell mediator release depends on their severity. The use of benzodiazepines, anti-histamines (H1 and H2 blockers), and corticosteroids is probably helpful in reducing the frequency and/or severity of symptoms related to mast cell mediator release.[202,203] Other options include fluid resuscitation, intravenous epinephrine, and discontinuation of the suspected drug or anesthetic agent.[202] The risk of anaphylaxis in the perioperative period is estimated to be higher in patients with SM relative to the general population.[204] In the event of anaphylaxis or other mast cell activation event, a full allergic workup should be initiated.[204,205] 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 to 120 minutes of symptom onset and also after full recovery.[202,203]

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.[206] 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 females with mastocytosis.[207-209] Symptoms related to mast cell mediator release have been observed in 11% of patients without any fatal outcome.[209]

SM is not a contraindication to a successful pregnancy. Patients with SM who are pregnant should be treated by a multidisciplinary team, including a high-risk obstetrician and anesthesiologist during the pre-conception, pregnancy, and 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. Breastfeeding 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, antihistamines, and epinephrine) are standard approaches during pregnancy and the early postpartum period.[210-212] Cytoreductive therapy with peginterferon alfa-2a is an option for patients who are pregnant with severe SM refractory to conventional therapy, although there are limited data regarding the use of peginterferon alfa-2a in pregnancy. It should be used only if benefits outweigh potential risk to the fetus.[213] However, the use of cladribine, imatinib, midostaurin, and avapritinib is not recommended. Medications used to treat SM and their potential risks during both pregnancy and lactation are summarized in the algorithm.

COVID-19 Vaccination

Patients with mast cell leukemia are a unique population with the potential for mast cell activation and/or anaphylaxis with the COVID-19 vaccines. Recommendations from the ECNM and the American Initiative in Mast Cell Diseases were recently published and some general recommendations are listed below.[214] Patients deemed at high risk for vaccination include those who have previously experienced grade 1 or 2 anaphylaxis, per Brighton consensus, after the first COVID-19 shot; those with known or suspected allergy to polyethylene glycol (PEG) or polysorbate 80/20; those with prior anaphylaxis following vaccination; and those with unstable mastocytosis and severe MCAS symptoms that are not controlled. Such patients should have two epinephrine autoinjectors with them and should receive the vaccine at a location with emergency awareness and that has equipment and drugs for resuscitation available. These individuals may also be evaluated by skin testing for vaccine components, such as PEG or polysorbate 80/20. Additionally, H1 antihistamine premedication should be used in these patients 1 hour before receiving the vaccine. Following vaccination, patients should also be supervised for 60 minutes.

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