Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-303-z Midostaurin

Stand: November 2023

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Midostaurin
[aggressive systemische Mastozytose (ASM), systemische Mastozytose mit assoziierter hämatologischer Neoplasie (SM-AHN) oder Mastzellleukämie (MCL)]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Allogene Stammzelltransplantation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** • Avapritinib: Beschluss vom 15.09.2022 • Midostaurin: Beschluss vom 05.04.2018 **Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use); Teil A:** • IV. Dinatriumcromoglycat (DNCG)-haltige Arzneimittel (oral) bei systemischer Mastozytose **Anlage I zum Abschnitt F der Arzneimittel-Richtlinie Gesetzliche Verordnungsausschlüsse in Arzneimittelversorgung und zugelassene Ausnahmen; Zugelassene Ausnahmen zum gesetzlichen Verordnungsausschluss nach § 34 Abs. 1 Satz 2 SGB V (OTC-Übersicht)** 15. Dinatriumcromoglycat (DNCG)-haltige Arzneimittel (oral) nur zur symptomatischen Behandlung der systemischen Mastozytose
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Midostaurin L01EX10 Rydapt	Rydapt wird angewendet: • […] • als Monotherapie zur Behandlung erwachsener Patienten mit aggressiver systemischer Mastozytose (ASM), systemischer Mastozytose mit assoziierter hämatologischer Neoplasie (SM-AHN) oder Mastzellleukämie (MCL).
Avapritinib L01EX18 Ayvakyt	Fortgeschrittene systemische Mastozytose (AdvSM) Ayvakyt ist als Monotherapie zur Behandlung erwachsener Patienten mit aggressiver systemischer Mastozytose (ASM), systemischer Mastozytose mit assoziierter hämatologischer Neoplasie (SM-AHN) oder Mastzellleukämie (MCL) nach zumindest einer systemischen Therapie indiziert.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2023-B-303-z (Midostaurin)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	1. November 2022

Inhaltsverzeichnis

Abkürzungsverzeichnis

ASM	Aggressive Systemic Mastocytosis
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CM	Cutaneous Mastocytosis
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HCT	Hematopoietic cell transplantation
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISM	Indolent Systemic Mastocytosis
KI	Konfidenzintervall
LoE	Level of Evidence
MCL	Mast Cell Leukemia
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
SM	Systemic mastocytosis
SM-AHN	Systemic Mastocytosis with an Associated Hematologic Neoplasm
SSM	Smoldering Systemic Mastocytosis
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Erwachsene mit aggressiver systemischer Mastozytose (ASM), systemischer Mastozytose mit assoziierter hämatologischer Neoplasie (SM-AHN) oder Mastzellleukämie (MCL).

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Mastozytose und Mastzellleukämie durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 25.10.2022 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 81 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf wurde insgesamt 1 Referenz eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenz.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Es wurden keine relevanten systematischen Reviews identifiziert.

3.3 Leitlinien

National Comprehensive Cancer Network (NCCN), 2022 [1].

Systemic Mastocytosis: Version 2.2022

Zielsetzung/Fragestellung

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Systemic Mastocytosis provide recommendations for the diagnosis and management of patients with SM. Management of Cutaneous Mastocytosis is not included in these guidelines.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium – trifft teilweise zu (Patientenbeteiligung unklar, VertreterInnen aus verschiedenen Fachrichtungen beteiligt);
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft nicht zu (siehe Recherche/Suchzeitraum);
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – unklar;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft teilweise zu (Evidenz über Hintergrundtext identifizierbar);
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

Recherche/Suchzeitraum:

- an electronic search of the PubMed database was performed to obtain key literature on SM published since the previous Guidelines update

LoE/GoR

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.
- For the 'uniform NCCN consensus' defined in Category 1 and Category 2A, a majority Panel vote of at least 85% is required. For the 'NCCN consensus' defined in Category 2B, a Panel vote of at least 50% (but less than 85%) is required. Lastly, for recommendations where there is strong Panel disagreement regardless of the quality of the evidence, NCCN requires a Panel vote of at least 25% to include and designate a recommendation as Category 3. The large majority of the recommendations put forth in the Guidelines are Category 2A. Where categories are not specified within the Guidelines, the default designation for the recommendation is Category 2A.

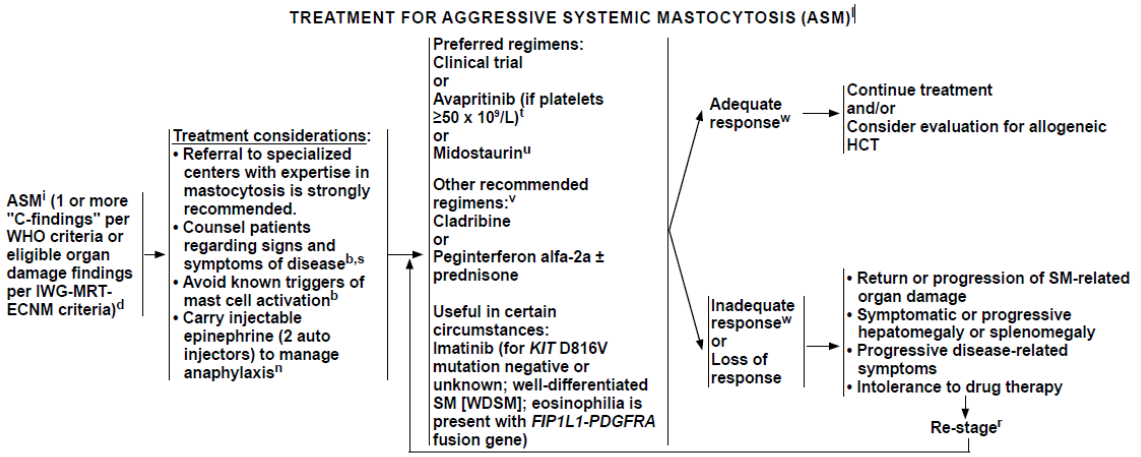
NCCN Categories of Preference

- 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).

<u>Sonstige methodische Hinweise</u>

- Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz wird die LL jedoch ergänzend dargestellt.
- Discussion last updated: October 18th, 2022.

Treatment for Aggressive Systemic Mastocytosis (ASM)

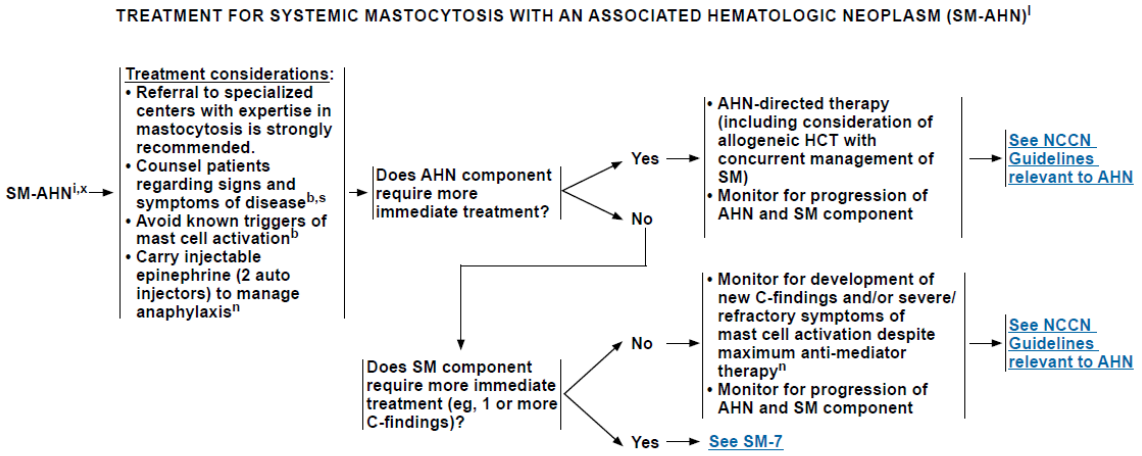


[b] Patients should be counseled about the signs/symptoms and potential triggers of mast cell activation (See SM-I). Multidisciplinary collaboration with sub-specialists (eg, anesthesia for procedures/ surgery; high-risk obstetrics for pregnancy) is recommended (SM-K).
[d] See WHO Criteria for B-Findings and C-Findings in Patients with Systemic Mastocytosis (SM-D) and IWG-MRT-ECNM Criteria for Eligible Organ Damage to Assess Clinical Improvement (CI) and Treatment Response (SM-E). B- and C-findings are used for the diagnosis of the WHO subtype of SM (SM-C and SM-D) and IWG-MRT-ECNM criteria are used to establish eligible organ damage findings for clinical trial enrollment and to adjudicate response to therapy (SM-E).
[i] See 2017 Diagnostic Criteria for the Variants of Systemic Mastocytosis (SM-C).
[l] See Adverse Prognostic Variables and Risk Stratification in Systemic Mastocytosis (SM-H).
[n] See (SM-J) 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] Taylor F, et al. Leuk Res 2021;108:106606.
[t] Avapritinib is not recommended for the treatment of patients with advanced SM with platelet counts of less than 50 X 10⁹/L. For the management of avapritinib toxicity, see SM-M.
[u] For management of midostaurin toxicity, see SM-L.
[v] 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.
[w] See 2013 IWG-MRT-ECNM Consensus Response Criteria (SM-F). Clinical benefit may not reach the threshold of the 2013 IWG-MRT-ECNM response criteria.

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.

SM-5

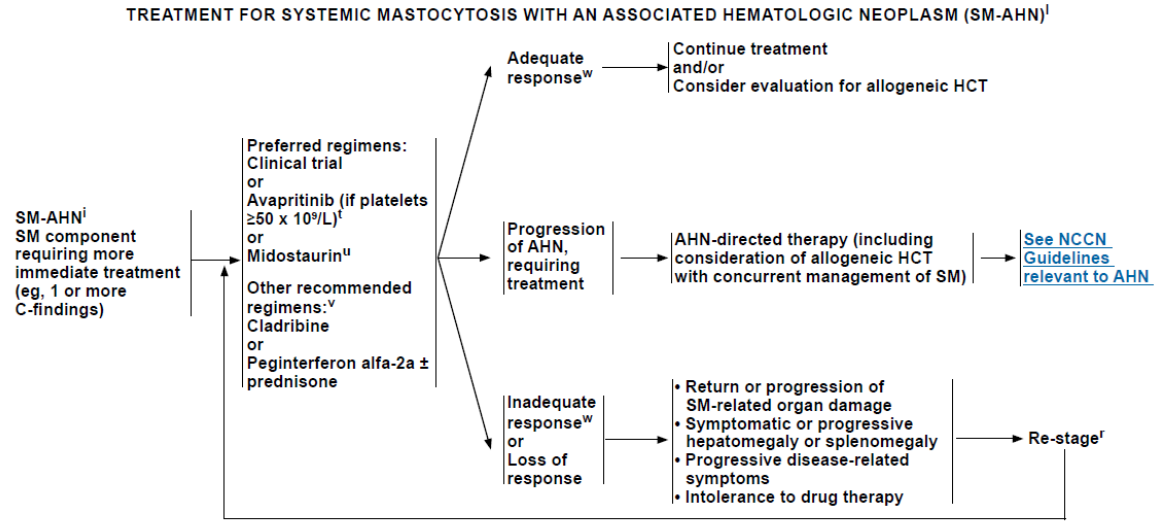
Treatment for Systemic Mastocytosis with an Associated Hematologic Neoplasm (SM-AHN)



[b] Patients should be counseled about the signs/symptoms and potential triggers of mast cell activation (See SM-I). Multidisciplinary collaboration with sub-specialists
[s] Taylor F, et al. Leuk Res 2021;108:106606.
[i] See 2017 Diagnostic Criteria for the Variants of Systemic Mastocytosis (SM-C).
[l] See Adverse Prognostic Variables and Risk Stratification in Systemic Mastocytosis (SM-H).
[n] See (SM-J) for anti-mediator drug therapy approaches for mast cell activation symptoms.
[x] These algorithms refer to SM-AHN with myeloid neoplasms, which comprise the majority of cases.

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.

SM-6



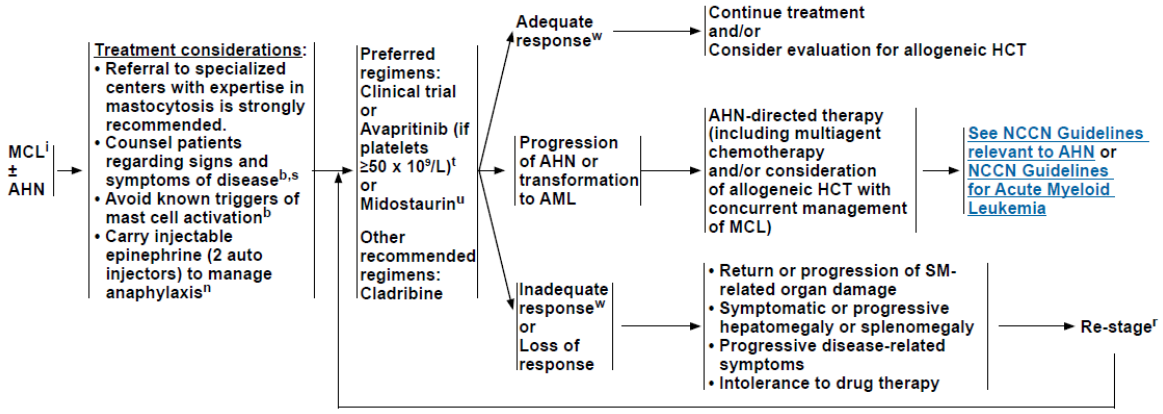
[i] See 2017 Diagnostic Criteria for the Variants of Systemic Mastocytosis (SM-C).
[l] See Adverse Prognostic Variables and Risk Stratification in Systemic Mastocytosis (SM-H).
[r] Bone marrow aspirate and biopsy, serum tryptase level, and additional staging studies should be performed as clinically indicated (if supported by increased symptoms and signs of progression). See Discussion.
[t] Avapritinib is not recommended for the treatment of patients with advanced SM with platelet counts of less than 50 X 10^9/L. For the management of avapritinib toxicity, see SM-M.
[u] For management of midostaurin toxicity, see SM-L.
[v] 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.
[w] See 2013 IWG-MRT-ECNM Consensus Response Criteria (SM-F). Clinical benefit may not reach the threshold of the 2013 IWG-MRT-ECNM response criteria.

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.

SM-7

Treatment for Mast Cell Leukemia (MCL)

TREATMENT FOR MAST CELL LEUKEMIA (MCL)[l,y]



[b] Patients should be counseled about the signs/symptoms and potential triggers of mast cell activation (See SM-I). Multidisciplinary collaboration with sub-specialists (eg, anesthesia for procedures/surgery; high-risk obstetrics for pregnancy) is recommended (See SM-K).
[i] See 2017 Diagnostic Criteria for the Variants of Systemic Mastocytosis (SM-C).
[l] See Adverse Prognostic Variables and Risk Stratification in Systemic Mastocytosis (SM-H).
[n] See (SM-J) 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] Taylor F, et al. Leuk Res 2021;108:106606.
[t] Avapritinib is not recommended for the treatment of patients with advanced SM with platelet counts of less than 50 X 10^9/L. For the management of avapritinib toxicity, see SM-M.
[u] For management of midostaurin toxicity, see SM-L.
[w] See 2013 IWG-MRT-ECNM Consensus Response Criteria (SM-F). Clinical benefit may not reach the threshold of the 2013 IWG-MRT-ECNM response criteria.
[y] Patients with chronic MCL have no organ damage. However, treatment should be considered given the poor prognosis of MCL.

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.

SM-8

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 (water-soluble cream 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 (water-soluble cream 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
  - H2 antihistamines
  - Topical cromolyn sodium (cream/ointment 1%–4%)[c]
- Continuous moderate symptoms
  - Scheduled non-sedating H1 antihistamines
    - ◊ Add sedating H1 antihistamines on demand
  - Scheduled or on-demand H2 antihistamines
  - Scheduled topical cromolyn sodium (cream/ointment 1%–4%)[c]
- Severe symptoms
  - Scheduled non-sedating H1 antihistamines
  - Scheduled sedating H1 antihistamines
  - Scheduled H2 antihistamines
  - Add anti-leukotrienes in refractory cases

Diffuse Forms with Life-Threatening Mast Cell-Mediated Related Symptoms, Bullae, and Blistering
- Treatment may require hospitalization
- Sterile conditions
- Topical 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.

Continued

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.

SM-J
1 OF 4

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

Organ Involvement/Symptoms	Stepwise Treatment[d,e]
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.
[d] Standard doses need to be titrated. Higher doses may be necessary for symptoms refractory to standard-dose treatment.
[e] The use of these medications in a stepwise treatment plan may vary according to the specific patient scenarios.

Continued

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.

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 before starting 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

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.

Discussion

Treatment Considerations

Referral to specialized centers with expertise in the management of mastocytosis is strongly recommended.4-6 Multidisciplinary collaboration with subspecialists (eg,

anesthesiologists for invasive procedures/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.32

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 activation112 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. Patient-reported outcome instruments are currently under development for patients with advanced SM.112 The advanced systemic mastocytosis symptom assessment form (AdvSM-SAF) is a 10-item diary that assesses the severity of the following symptoms: abdominal pain, nausea, vomiting, diarrhea, spots, itching, flushing, and fatigue.112 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.

Cytoreductive therapy with avapritinib, midostaurin, cladribine, or peginterferon alfa-2a (discussed below) for rapid debulking of disease are options for patients with advanced SM (ASM, SM-AHN, and MCL) owing to the frequent presence of organ damage and shortened survival of this patient population. However, cladribine or peginterferon alfa-2a may also be useful in selected patients with ISM or SSM with severe, refractory symptoms related to mast cell mediator release or bone disease not responsive to anti-mediator drug therapy or bisphosphonates. Given the potential toxicities associated with cladribine therapy, including drugrelated 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 more immediate treatment. This determination can be challenging and reflects a comprehensive evaluation of several factors, including the relative burden and/or stage of the SM and AHN disease components in the bone marrow and/or other extracutaneous organs. In some cases, organ-directed biopsy may be useful to determine whether organ damage is related to the SM or AHN or both (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,39-41 cytoreductive therapy should still be considered for such patients given the poor prognosis of both MCL subtypes.

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

Anti-Mediator Drug Therapy

Management of Chronic Symptoms Related to Mast Cell Mediator Release

A stepwise treatment approach for specific symptoms should be considered for all patients who present with symptoms related to mast cell mediator release, as outlined in the algorithm on SM-J.113 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).114

Cromolyn sodium is effective for the management of cutaneous, gastrointestinal, and neurological symptoms.115-118 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.115 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.116 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.117,118

Aspirin, corticosteroids, and leukotriene receptor antagonists are useful for the management of symptoms that are refractory to other treatment options.114 In particular, leukotriene receptor antagonists have been used for the management of skin and gastrointestinal symptoms that have not responded to other therapies.119,120 Aspirin has been shown to be effective for the management of symptoms associated with elevated urinary prostaglandin levels.121 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.122-128 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.129 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.29,130,131 Increased serum tryptase levels have been identified as a risk factor for anaphylaxis in some studies,29,132 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.132-134

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.135,136 Hymenoptera venom allergy is an established risk factor for severe recurrent anaphylaxis in patients with SM.137 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.138 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.139-142 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.141 KIT

D816V mutation has been implicated in the hyperactivity of mast cells by amplifying the IgE-dependent mast cell mediator release.143 However, the exact mechanism of increased susceptibility to Hymenoptera venom anaphylaxis has not been elucidated in patients with SM.

Anaphylactic symptoms should be treated with epinephrine as first-line therapy. Antihistamines (H1 and H2 blockers) and steroids can be added as required. Systemic hives with no organ involvement can be managed with the use of antihistamines. Epinephrine injection is the preferred treatment for systemic hives with organ involvement (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.136

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.144-147 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.136

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.122-124 Omalizumab can also improve tolerance while on VIT.

Cytoreductive Therapy

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

Avapritinib156,157 and midostaurin158-160 are preferred regimens and cladribine161-163 is an “other recommended regimen” for patients with ASM, SM-AHN (when the SM component requires more immediate treatment), and MCL (with or without an associated hematologic neoplasm). Imatinib is included as a treatment option for patients with ASM (for KIT D816V mutation negative or unknown, WDSM, or if eosinophilia is present with FIP1L1-PDGFRA fusion gene).19,164-170

Data from clinical trials that evaluated avapritinib, midostaurin, cladribine, and imatinib in patients with SM are discussed below.

Interferon alfa (with or without prednisone) can 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.171-174 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.

Peginterferon alfa-2a ± prednisone is included as an “other recommended regimen” for patients with ASM and SM-AHN (when the SM component requires more immediate treatment).

Avapritinib

Avapritinib, a potent and selective inhibitor of KIT D816V, has demonstrated activity in patients with advanced SM.157

Data from the phase I EXPLORER trial, which consisted of 53 evaluable patients with advanced SM (3 patients with ASM, 37 patients with SMAHN, and 13 patients with MCL),

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 modified IWG-MRT-ECNM (mIWG-MRT-ECNM) response criteria.156 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 nonhematologic 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%).

A pre-specified interim analysis of the phase II PATHFINDER trial consisted of 32 evaluable patients with advanced SM: 2 patients with ASM, 26 patients with SM-AHN, and 4 patients with MCL.157 Using the mIWG-MRT-ECNM response criteria, treatment with avapritinib resulted in an ORR of 75% (95% CI, 57%–89%). 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 alkaline phosphatase (5%), peripheral edema (3%), periorbital edema (3%), and fatigue (3%).

Avapritinib is U.S. Food and Drug Administration (FDA)-approved for the treatment of adult patients with advanced SM, including ASM, SM-AHN, and MCL. An ongoing phase II trial is investigating the efficacy and safety of avapritinib in patients with indolent SM with symptoms that are inadequately controlled by best supportive care.175

Comparison between avapritinib and best available therapy was performed in one study that pooled data from a multi-center study whereby patients with AdvSM were treated with best available therapy and data from the EXPLORER and PATHFINDER trials.176 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 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).177 OS was also improved in patients with SM-AHN treated with avapritinib compared to best available therapy.178 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 AdvSM treated with avapritinib.176 The efficacy of avapritinib in patients with AdvSM was established irrespective of prior therapies or S/A/R mutation status.179

Midostaurin

Midostaurin, an oral multikinase inhibitor, has demonstrated activity for the treatment of advanced SM (ASM, SM-AHN, and MCL).158-160

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).158 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.

Midostaurin is approved by the FDA 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 2 clinical trial.180

A recent study that evaluated the impact of KIT D816V mutation and other molecular markers on the clinical outcome of 38 patients with advanced SM treated with midostaurin found that the ORR, median duration of midostaurin treatment, and OS were significantly higher in patients with an S/A/Rneg (vs. S/A/Rpos) mutation profile and in patients with a greater than or equal to 25% (vs. <25%) reduction in the KIT D816V allele burden using ASO-qPCR.181 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 quality of life and mast cell mediator-related symptoms in patients with advanced SM who were treated with midostaurin.182

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.161-163 Cladribine may be particularly useful for patients with advanced SM when rapid debulking of disease is required.

In an analysis, 108 patients with SM treated with cytoreductive therapy, cladribine, resulted in an ORR of 56%, 50%, and 55%, respectively, in patients with ISM, ASM, and SM-AHN.162 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%).163 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 greater than 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.

Imatinib

Imatinib is very effective in the treatment of patients with eosinophilia-associated myeloid neoplasms characterized by the FIP1L1-PDGFRA fusion tyrosine kinase.88,89 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 9.19,164-170 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.19

Imatinib is approved by the FDA for the treatment of adult patients with ASM without the KIT D816V mutation (including wild-type) or with unknown mutational status.

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.183-185 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% for patients with SM-AHN; 43% and 17%, respectively, for patients with ASM and MCL).185 MCL subtype was the strongest risk factor for poor OS. The role of allogeneic HCT needs to be determined in a prospective trial. However, given the rarity of SM, no larger prospective trials of HCT have been initiated to confirm the role of allogeneic HCT. In 2016, a consensus opinion was published on indication for allogeneic HCT in patients with advanced SM.186

Evaluation for allogeneic HCT should be considered for patients with ASM and MCL if there is adequate response to initial treatment with cytoreductive therapy. Among patients with SM-AHN, allogeneic HCT should be considered as part of initial treatment when the AHN component requires HCT. It should also be considered if the SM component presents as advanced SM (and there is adequate response to initial treatment with cytoreductive therapy) or progresses to advanced SM during treatment. Prophylactic anti-mediator drug therapy (corticosteroids, antihistamines, and epinephrine) should be used with the conditioning regimen in all patients.186

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systemic.html?f=menu%3D6%2Abrowseby%3D8%2Asortby%3D2%2Ame
dia%3D3%2Ace_id%3D2233%2Aot_id%3D26855%2Amarker%3D1769% 2Afeatured%3D17676.
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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2022) am 25.10.2022

#	Suchfrage
1	MeSH descriptor: [Mast Cell Activation Disorders] explode all trees
2	(mastocytos* OR (("mast cell activation") NEXT (syndrome* OR disease* OR disorder*)) OR ("mast cell" NEXT (syndrome* OR disease* OR disorder*))):ti,ab,kw
3	(mastocytoma* OR (("mast cell" OR mastcell) NEXT (leukemia* OR leukaemia* OR leucemia* OR leucaemia* OR tumour* OR tumor* OR neoplas* OR sarcoma*))):ti,ab,kw
4	#1 OR #2 OR #3
5	#4 with Cochrane Library publication date from Oct 2017 to present, in Cochrane Reviews

Systematic Reviews in PubMed am 25.10.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	Mast Cell Activation Disorders[mh]
2	mastocytos*[tiab] OR ("mast cell activation"[tiab] AND (syndrome*[tiab] OR disease*[tiab] OR disorder*[tiab])) OR "mast cell syndrome*"[tiab] OR "mast cell disease*"[tiab] OR "mast cell disorder*"[tiab]
3	mastocytoma*[tiab] OR (("mast cell"[tiab] OR mastcell[tiab]) AND (leukemia*[tiab] OR leukaemia*[tiab] OR leucemia*[tiab] OR leucaemia*[tiab] OR tumour*[tiab] OR tumor[tiab] OR tumors[tiab] OR neoplas*[tiab] OR sarcoma*[tiab]))
4	#1 OR #2 OR #3
5	(#4) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw]

#	Suchfrage
	OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
6	(#5) AND ("2017/10/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in PubMed am 25.10.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	Mast Cell Activation Disorders[mh]
2	mastocytos*[tiab] OR ("mast cell activation"[tiab] AND (syndrome*[tiab] OR disease*[tiab] OR disorder*[tiab])) OR "mast cell syndrome*"[tiab] OR "mast cell disease*"[tiab] OR "mast cell disorder*"[tiab]
3	mastocytoma*[tiab] OR (("mast cell"[tiab] OR mastcell[tiab]) AND (leukemia*[tiab] OR leukaemia*[tiab] OR leucemia*[tiab] OR leucaemia*[tiab] OR tumour*[tiab] OR tumor[tiab] OR tumors[tiab] OR neoplas*[tiab] OR sarcoma*[tiab]))
4	#1 OR #2 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
6	(#5) AND ("2017/10/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 25.10.2022

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)

- Dynamed/EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **National Comprehensive Cancer Network (NCCN).** Systemic Mastocytosis, Version 2.2022 [online]. Plymouth Meeting (USA): NCCN; 2022. [Zugriff: 25.10.2022]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/mastocytosis.pdf.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.0

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2023-B-303-z

Kontaktdaten

Fachgesellschaften:

- Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

Indikation gemäß Beratungsantrag

Behandlung Erwachsener mit aggressiver systemischer Mastozytose (ASM), systemischer Mastozytose mit assoziierter hämatologischer Neoplasie (SM-AHN) oder Mastzellleukämie (MCL).

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

<u>Zusammenfassung</u>

Die systemische Mastozytose (SM) ist eine seltene hämatologische Neoplasie. Sie wird in die fortgeschrittene SM (engl.: „advanced“, AdvSM) mit sehr schlechter Prognose und die Nicht-AdvSM (indolente SM [ISM] und smoldering SM [SSM]) mit in der Regel normaler Lebenserwartung unterteilt (ein Teil der Patientinnen und Patienten (Pat.) mit ISM und SSM können im Verlauf eine AdvSM entwickeln). Die AdvSM wird in drei Subtypen unterteilt: die am häufigsten vorkommende SM mit assoziierter hämatologischer Neoplasie (SM-AHN), sowie die selteneren Subtypen aggressive SM (ASM) und Mastzellleukämie (MCL) [1-3]. In der überwiegenden Zahl der Fälle (>90%) ist eine aktivierende Mutation (vorwiegend D816V) in der Tyrosinkinase *KIT* (auch CD117, c-Kit oder Stammzellfaktor-Rezeptor) nachweisbar, die als krankheitsinitiierend gilt. Für Diagnose und Verlaufsbeurteilung sehr wichtig ist eine bei nahezu allen Pat. mit AdvSM im Serum nachweisbare Erhöhung der von Mastzellen produzierten Tryptase. Durch verbesserte Diagnostik und durch erhöhte Aufmerksamkeit versorgender Ärzte (z.B. häufigere Tryptase-Bestimmung, Nachweis der *KIT* D816V Mutation z.B. im Rahmen von NGS-Diagnostik) ist in den letzten Jahren eine zunehmende Zahl an Pat. mit AdvSM in Deutschland diagnostiziert worden [4].

Bei Pat. mit AdvSM führt die Organinfiltration der SM-Zellen und der in vielen Fällen vorliegenden AHN zu Organdysfunktionen und einer Vielzahl pathologischer Befunde (dies werden als sogenannte C-Findings bezeichnet, ihr Vorliegen definiert z.B. die ASM: Anämie, Thrombozytopenie, Leberfunktionsstörung, Hypersplenismus mit Zytopenie, Malabsorption mit Gewichtsverlust, sehr selten auch große Osteolysen mit pathologischen Frakturen). Daneben kommt es durch unkontrollierte Freisetzung von Mastzell-Botenstoffen zu hoher Symptomlast bei den Pat. (z.B. Fatigue, Juckreiz, Diarrhö, Tenesmen etc.).

Bis zur Einführung einer zielgerichteten Therapie mit dem KIT-/Multikinase-Inhibitor Midostaurin durch die FDA (2016) und die EMA (2017) gab es keine zugelassene medikamentöse Therapie zur Behandlung der Pat. mit AdvSM. Daher kamen z.B. Cladribin oder (sehr viel seltener) Interferon-alpha und andere, bei myeloischen Neoplasien häufiger eingesetzte Substanzen wie z.B. Hydroxyurea, oder, bei sehr aggressivem Verlauf, eine AML-typische intensive Chemotherapie zum Einsatz. Da die *KIT* D816V Mutation

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gegenüber dem Tyrosinkinase-Inhibitor Imatinib primär resistent ist, könnte Imatinib nur in sehr seltenen Fällen (<5%) einer *KIT* D816V negativen SM eingesetzt werden [5].

Die Wirksamkeit der oben dargestellten nicht-zugelassenen Therapien wurde lediglich in retrospektiven Fallserien und nicht-randomisierten Studien an kleinen, meist inhomogenen Patientenkollektiven gezeigt. Midostaurin konnte in einer einarmigen Phase-II Zulassungsstudie die extrem schlechte Prognose und den Verlauf der AdvSM-Erkrankung nachhaltig verbessern.

Bei Therapieversagen nach oder Nichtansprechen auf Midostaurin (oder bei Unverträglichkeit gegenüber Midostaurin) steht jetzt mit Avapritinib das erste, von der EMA zugelassene Arzneimittel zur Verfügung. Es ist zugelassen zur Behandlung der AdvSM mit den Subtypen ASM, SM-AHN und MCL, nach zumindest einer systemischen Vortherapie [6, 7]. Weitere Therapieoptionen sind Cladribin sowie seltener andere Chemotherapeutika [5, 6]. Die allogene Stammzelltransplantation kann aufgrund des in der Regel hohen Patientenalters leider nur in seltenen Fällen durchgeführt werden und ist zudem aufgrund der Therapieresistenz maligner Mastzellen mit einem hohen Rezidivrisiko assoziiert.

<u>Fragestellung</u>

Die Fragestellung ist sehr weit gefasst. Es werden die aktuellen Therapieoptionen diskutiert.

<u>Stand des Wissens</u>

Der für Deutschland aktuelle Behandlungsstandard ist in den folgenden Abbildungen dargestellt [9]:

Abbildung 1: Therapiestruktur der SM:

Kontaktdaten

Fachgesellschaften:

- Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

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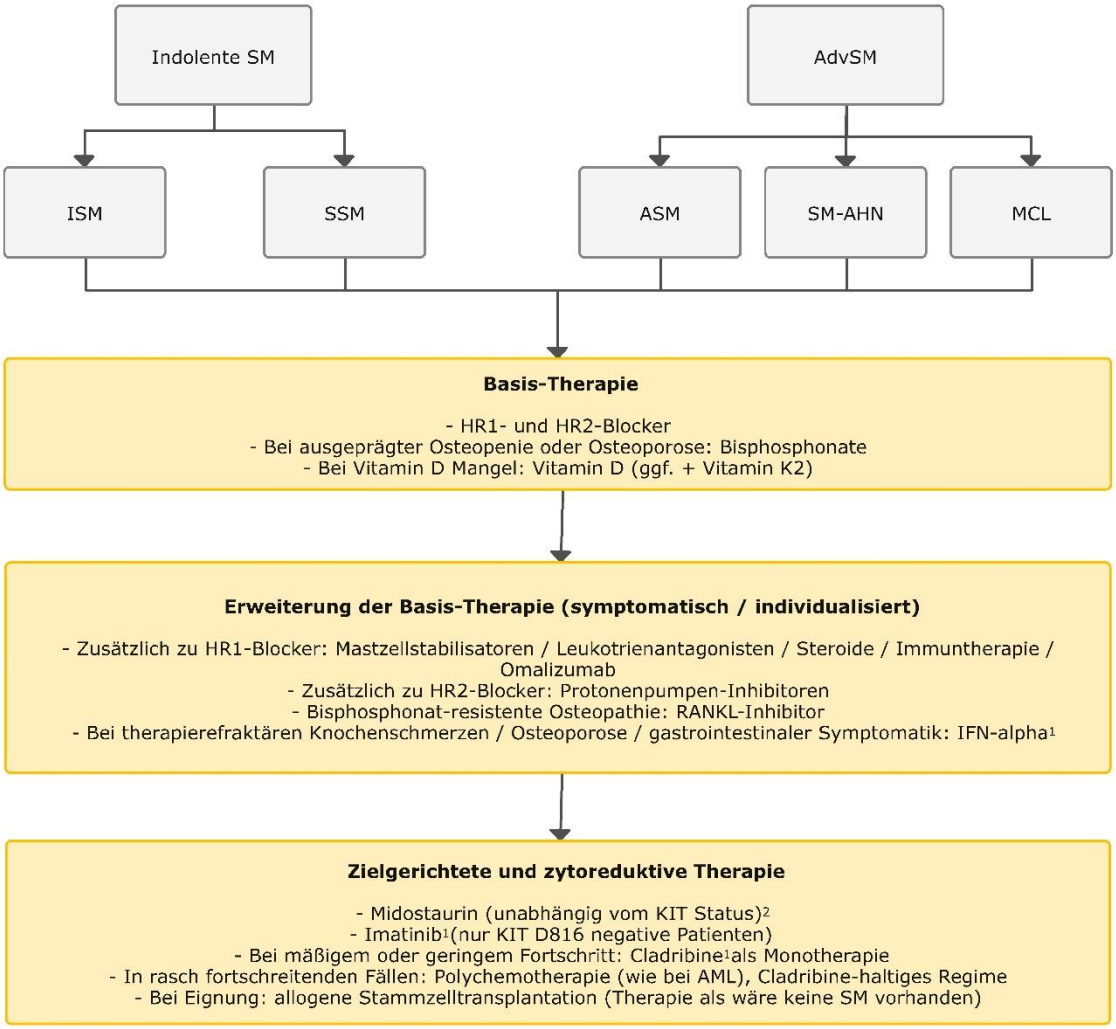

ISM, indolente SM; SSM, smoldering SM; ASM, aggressive SM; SM-AHN, SM mit assoziierter hämatologischer Neoplasie; MCL, Mastzell-Leukämie.[1] nur off-label; [2] insbesondere bei hoher KIT D816V Mutationslast, z.B. ≥5-10%

im peripheren Blut und Nachweis einer AdvSM sollte Midostaurin im Therapiemanagement (ggf. additiv) berücksichtigt werden. https://www.onkopedia.com

Abbildung 2:

Kontaktdaten

Fachgesellschaften:

- Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

Indikation gemäß Beratungsantrag

Behandlung Erwachsener mit aggressiver systemischer Mastozytose (ASM), systemischer Mastozytose mit assoziierter hämatologischer Neoplasie (SM-AHN) oder Mastzellleukämie (MCL).

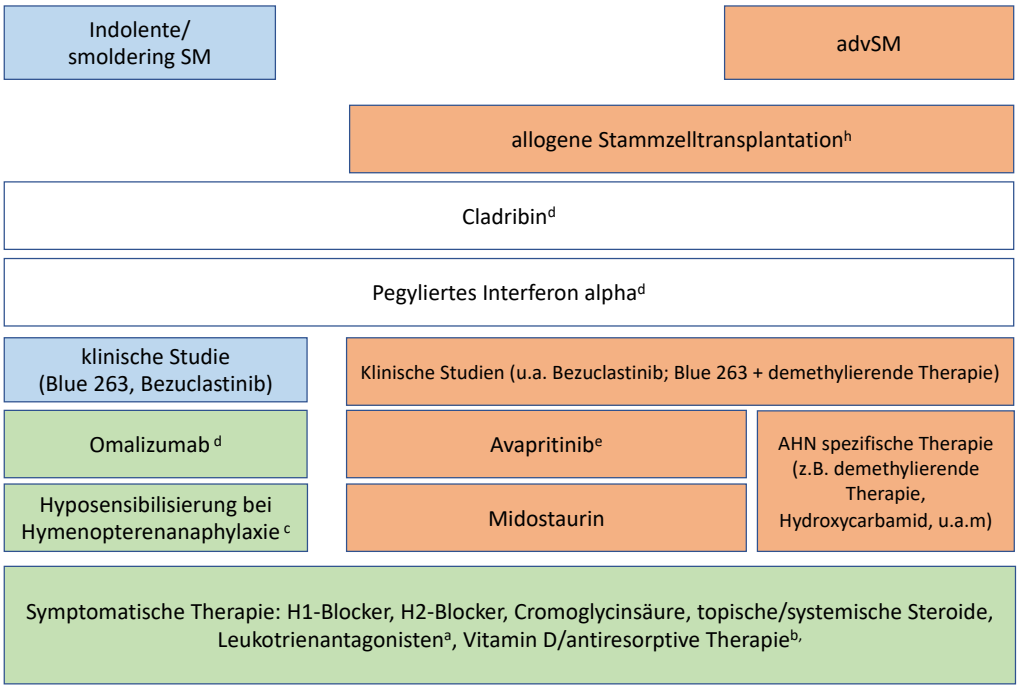

Abb. 2: Therapiealgorithmus systemische Mastozytose: symptomatische Basistherapie (grün), Therapie der indolenten Formen (blau), Therapie der AdvSM (grün). [a]Einsatz bei pulmonaler Symptomatik, [b]nach Leitlinie Osteologie, [c]Hyposensibilisierung lebenslang, [d]off-label Use, [e]Einsatz ab 2.Linie

Midostaurin, ein oraler KIT-/Multikinase-Inhibitor, ist das einzige in Deutschland zugelassene Medikament zur Therapie der AdvSM. In etwa 60% der Fälle kommt es zu einem Ansprechen (Besserung der C-Findings, Tryptaseabfall) mit begleitender Reduktion der Mastzellinfiltration im Knochenmark, Rückgang der Milzgröße und der *KIT* D816V Mutationslast [10-12]. Bei einigen Pat. kommt es zu einer jahrelangen Stabilisierung der Erkrankung. Andererseits werden aber auch Pat. mit primärer Resistenz und frühem Krankheitsfortschreiten (Progression) beobachtet. Etablierte Faktoren, die das Ansprechen auf eine Therapie mit Midostaurin negativ beeinflussen sind:

- der Nachweis prognostisch ungünstiger somatischen Mutationen in *SRSF2*, *ASXL1* oder *RUNX*1 (*S*/*A*/*R*) [13]

Kontaktdaten

Fachgesellschaften:

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Indikation gemäß Beratungsantrag

Behandlung Erwachsener mit aggressiver systemischer Mastozytose (ASM), systemischer Mastozytose mit assoziierter hämatologischer Neoplasie (SM-AHN) oder Mastzellleukämie (MCL).

- und das Nichterreichen einer mindestens <25%-igen Reduktion der *KIT* D816V Mutationslast innerhalb der ersten 6 Monate der Behandlung.

Die Verträglichkeit der Substanz kann im Einzelfall zu fehlender Therapieadhärenz führen. Midostaurin (Rydapt) ist in der für AdvSM vorgesehenen Dosierung von 2 x 100 mg oft mit Übelkeit und Erbrechen durch den für manche Pat. sehr unangenehmen Geruch und Geschmack verbunden. Daher ist eine konsequente, in der Regel auch dauerhafte antiemetische Therapie (z.B. mit 5HT-3 Antagonisten, gelegentlich auch mit oralen Kortikosteroiden) zwingend erforderlich. Eine Missachtung dieser Ko-Medikation führt sehr häufig zum Therapieabbruch [14].

Cladribin führt unabhängig von einer Vortherapie mit Midostaurin zu einem Ansprechen in 40-70% der Fälle. In der Regel ist das Ansprechen aber nur partiell und auch die Dauer des Ansprechens ist häufig begrenzt (Wochen bis Monate) [15-17]. Protrahierte Zytopenien und opportunistische Infektionen sind als mögliche Komplikationen zu beachten. Kürzlich konnte eine signifikante Unterlegenheit im Vergleich zur Behandlung mit Midostaurin sowohl in der Erstlinie als auch bei Pat. mit Vortherapie gezeigt werden [18]

Sogenannte intensive Induktionschemotherapien kommen, angelehnt an Protokolle für die *de novo* AML, bei rasch fortschreitender oder therapierefraktärer AdvSM und SM-AML zum Einsatz. Induktionstherapien machen allerdings nur bei Möglichkeit zur anschließenden allogenen Stammzelltransplantation zu Therapiekonsolidierung bei geeigneten Pat. mit gutem Ansprechen Sinn.

Die **allogene Stammzelltransplantation (SZT)** ist die einzige potentiell kurative Therapieform bei Pat. mit AdvSM. Für eine allogene SZT kommt aufgrund des hohen medianen Patientenalters und des oft schlechten Allgemeinzustandes von Pat. mit advSM nur eine Minderheit der Pat. infrage. Ihre Wertigkeit ist aufgrund fehlender prospektiver Studien nicht geklärt. In retrospektiven Analysen mit kleinem und heterogenem Patientenkollektiv lag das 3-Jahres-Gesamtüberleben bei 57% für alle Pat., 74% für SM-AHN, 43% für ASM und 17% für MCL [19, 20].

Avapritinib ist ein spezifischer KIT-Inhibitor. Es ist seit März 2022 durch die EMA zugelassen und kann in Deutschland bei Pat. mit AdvSM nach einer vorangegangen Systemtherapie erfolgen. Während die Ende 2021 erteilte Zulassung der FDA eine Gabe im First- und Second/bzw. Furtherline Setting erlaubt, kann dies, wie oben beschrieben, in Deutschland erst nach Vortherapie, z.B. Midostaurin oder Cladribin, geschehen. Die Zulassung basiert auf den Ergebnissen zweier nicht-randomisierter Phase-I- bzw. II-Studien EXPLORER und PATHFINDER mit 86 bzw. 62 Pat, in die Pat. mit und ohne Vorbehandlung eingeschlossen wurden. Die Auswertung des Ansprechens wurde jeweils bei 53 (davon 32 vorbehandelt) und 32 (davon 23 vorbehandelt) Pat. mit evaluierbarem Ansprechen durchgeführt: Avapritinib führte in beiden Studien zu Gesamtansprechraten von 75%, zu einer signifikanten Reduktion aller Krankheits-assoziierter Befunde (z.B. Knochenmarkinfiltration, Serum-Tryptase, Splenomegalie, KIT D816V Mutationslast, s.u.) sowie zu einer signifikanten Verbesserung der Krankheits-assoziierten Symptome und der Lebensqualität. Insgesamt erreichten 36% (EXPLORER) und 19% (PATHFINDER) der Pat. eine komplette Remission bzw. eine

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komplette Remission mit inkompletter Normalisierung des Blutbildes. Des Weiteren zeigte sich in beiden Studien eine signifikante (>50%ige) Reduktion der Mastzellinfiltration im Knochenmark (92% vs. 88%) und der Mastzelltryptase im Serum (99% vs. 93%) sowie der *KIT* D816V Mutationslast (80% vs. 60%). Das Ansprechen in der Zweitlinien- unterschied sich nicht signifikant vom dem in der Erstlinientherapie. Die Wirksamkeit von Avapritinib speziell in der Zweitlinientherapie wurde in einer aktuellen Analyse der gepoolten Daten beider Studien genau untersucht [7]. In einer weiteren aktuellen Studie wurde Avapritinib mit der bestmöglichen Therapie (*engl.: „best availble therapy“*, BAT) verglichen [21]. Die Verbesserung der Krankheitsaktivitätsparameter übersetzte sich ferner in ein verbessertes Symptombild gemessen mittels standardisierter Fragebogenanalysen (AdvSM-SAF).

Neben der zytoreduktiven Therapie besteht bei einem großen Teil der Pat. auch die Indikation für eine Basistherapie bestehend aus H1- und H2-Blockern sowie mitunter auch von Mastzellstabilisatoren wie im Behandlungspfad oben gezeigt.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von Personen mit aggressiver systemischer Mastozytose (ASM), systemischer Mastozytose mit assoziierter hämatologischer Neoplasie (SM-AHN) oder Mastzellleukämie (MCL) die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Ja, diese sind oben dargestellt.

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