



Mastocytosis in clinical practice – current standards of care

Angelika Agnieszka Masiarz^{1,A-F}✉, Urszula Gawryś^{1,A-F}, Wiktoria Tochman^{1,A-F},
Monika Podhorecka^{1,A-F}

¹ Student Scientific Society of Department of Haematology and Bone Marrow Transplantation, Medical University, Lublin, Poland

² Department of Haematology and Bone Marrow Transplantation, Medical University, Lublin, Poland

A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Masiarz AA, Gawryś U, Tochman W, Podhorecka M. Mastocytosis in clinical practice – current standards of care. J Pre-Clin Clin Res. 2026;20(2):88–94. doi:10.26444/jpccr/221743

Abstract

Introduction and Objective. Mastocytosis is a rare, heterogeneous group of disorders characterized by clonal proliferation and accumulation of mast cells in various organs, most commonly the skin and bone marrow. The aim of the review is to summarize current knowledge on epidemiology, pathogenesis, diagnostic criteria and therapeutic strategies in mastocytosis, with special emphasis on novel targeted treatments.

Review Methods. A structured literature search was performed using PubMed, Scopus, and Web of Science. Articles published between January 2015 – October 2025 were included. This period was chosen to reflect recent advances in the understanding and treatment of mastocytosis, including developments in molecular diagnostics and targeted therapies. Relevant publications were selected based on their contribution to the topic, with emphasis on clinical relevance. Priority was given to clinical trials, reviews, and guidelines.

Brief description of the state of knowledge. The pathogenesis of mastocytosis is dominated by activating KIT mutations, primarily D816V, which stimulate mast cell proliferation and survival through JAK-STAT, MAPK and PI3K pathways. Additional mutations including TET2, ASXL1, SRSF2 and RUNX1 contribute to more aggressive disease and worse prognosis. Symptomatic therapy remains the foundation of management for most patients and includes H1/H2 antihistamines, leukotriene antagonists, proton pump inhibitors and mast cell stabilizers.

Summary. Advances in the understanding of molecular basis, improved diagnostic precision and the development of potent selective KIT inhibitors have transformed the management of mastocytosis. Symptomatic therapy remains essential for indolent forms, while targeted agents provide effective options for severe variants. Nevertheless, there is a need to further develop research in this area.

Key words

treatment options, mastocytosis, clinical standards

INTRODUCTION

The rare and diverse collection of illnesses known as mastocytosis is typified by the aberrant growth and accumulation of mast cells (MC) in different human tissues, most frequently in the skin, bone marrow, liver, spleen, and gastrointestinal system. It is a rare disease, and its clinical presentation is highly variable. Clinical manifestations range from minor cutaneous lesions to severe, life-threatening systemic forms [1]. This variability, together with the low prevalence, makes diagnosis difficult and often delayed. In addition, the symptoms are often nonspecific and may mimic other conditions, which further complicates the diagnostic process. Mastocytosis is mostly caused by somatic mutations in the KIT gene, which codes for the c-KIT receptor (CD117), which controls the proliferation and differentiation of mast cells. The most prevalent mutation, D816V, causes constitutive receptor activation and unchecked mast cell proliferation. KIT/CD117 receptor mutations were studied

as the typical changes for human mastocytosis, although their detection may require specialized methods and is not always available [2]. Cutaneous mastocytosis (CM) is characterized by an abnormal accumulation of mast cells in the skin. This includes the three recognised forms: diffuse cutaneous mastocytosis, cutaneous mastocytoma and, the most common form, maculopapular cutaneous mastocytosis. It predominantly affects children, with over 90% of paediatric mastocytosis cases involving only skin manifestations [3]. Systemic mastocytosis (SM) is the term used to describe the condition when cutaneous mastocytosis occurs in conjunction with mast cell infiltration of other extracutaneous organs. Mastocytosis epidemiology is still not fully understood, which further complicates diagnosis. One study from Sweden found an annual incidence of 1.56 per 100,000 and a prevalence of 23.9 per 100,000 [4]. The prevalence of SM in Europe is estimated between 1/7,700 – 1/10,400, confirming its rarity. Caucasians are disproportionately affected with SM, and there is no sex gender preponderance. SM primarily affects adults (the average age at diagnosis is 60 years old), and it is extremely uncommon in children [5]. In recent years, advances in molecular diagnostics and targeted therapies have improved the understanding and management of mastocytosis.

✉ Address for correspondence: Angelika Agnieszka Masiarz, Department of Haematology and Bone Marrow Transplantation, Medical University, Staszica 11, 20-081 Lublin, Poland
E-mail: masiarz.ang@gmail.com

However, treatment remains challenging and depends on disease severity and clinical presentation.

The aim of the review is to discuss the factors underlying the occurrence of mastocytosis and the currently used therapeutic strategies.

MATERIALS AND METHOD

The study is a narrative review aimed at providing an overview of mastocytosis. A structured literature search was performed using PubMed, Scopus, and Web of Science. Google Scholar was used as an additional source when needed. Articles published between January 2015 and October 2025 were included. This period was chosen to reflect recent advances in the understanding and treatment of mastocytosis, including developments in molecular diagnostics and targeted therapies. The search was based on the following key words: ‘mastocytosis’, ‘systemic mastocytosis’, ‘cutaneous mastocytosis’, ‘clonal mast cell disease’, ‘advanced systemic mastocytosis’, ‘indolent mastocytosis’, and treatment-related terms. Relevant publications were selected based on their contribution to the topic, with emphasis on clinical relevance. Priority was given to clinical trials, reviews, and guidelines.

Pathogenesis. The pathogenesis of mastocytosis is complex. It consists genetic mutations, cytokine signalling and micro-environmental factors causing dysregulation in mast cells population [1]. The key component of the pathogenesis of mastocytosis is the presence of mutations in the KIT gene, which codes for the tyrosine kinase receptor (CD117). This leads to constitutive activation of KIT signalling but also initiates cascades of signalling, such as the JAK-STAT, MAPK, and PI3K-AKT pathways, which support mast cell survival, proliferation, and apoptosis resistance. The most prevalent mutation is KIT D816V, which is found in over 90% cases of systemic mastocytosis [2]. There have also been reports of additional uncommon KIT mutations, including those in exons 8, 9, or 17 [6]. Bone marrow, peripheral blood, and infiltrating tissues can all be examined for this mutation using extremely sensitive and quantitative methods, such as allele-specific quantitative-real-time polymerase chain reaction (PCR) on mRNA or on DNA [7]. Further gene mutations, including those in TET2, SRSF2, ASXL1, and RUNX1, are often linked to severe disease and a poor prognosis [8]. The bone marrow and peripheral tissues offer a supportive environment that maintains mast cell expansion, and mast cell accumulation is caused by a number of triggers. Consequently, at different phases of stem cell development, Stem Cell Factor (SCF) plays a key role in regulating the proliferation, maturity, and survival of human MC stem cells and pluripotent MC progenitors [9]. Through certain receptors, SCF affects also all mature MC classes [10]. In addition, many cytokines have been shown to affect immature forms of mast cells. Among others, interleukins 3, 4, 6, 9, and 13 have been studied for their effect on progenitor cell expansion [1]. In vitro, it has been demonstrated that IL-3 increases the survival of mast cell progenitors. The survival and development of CD34+ progenitors were enhanced when they were cultured with IL-3 and IL-6 together, or with each cytokine independently. IL-6 decreases suppressor of cytokine signalling 3 to increase mast cell maturation, proliferation, and reactivity [11]. These results were associated

with elevated expression and activity of signal transducer and activator of transcription 3 (STAT3), as well as methylation of the suppressor of cytokine signalling 3 promoter [12]. Furthermore, IL-4 promotes mast cell proliferation by producing leukotrienes, and both IL-4 and IL-13 stimulate mast cell signalling pathways include MEK, AP-1, p-38, AKT, and SHP-1 [13]. According to another study, psychological stress also exacerbates several types of diseases, including mastocytosis. Interleukin-33 enhances the process by which neuropeptides, particularly corticotropin-releasing hormone, neurotensin, and substance P, stimulate MCs, which mediate this reaction [14].

Diagnostic criteria and classification. The initial clinical assessment involves taking a detailed medical history, including information on the presence of skin symptoms and the onset of systemic symptoms caused by mediators released by mast cells, as well as conducting a thorough physical examination, including an assessment of the skin. Characteristic maculopapular lesions with a positive Darier’s sign suggest mastocytosis, which is confirmed by histopathological examination. According to the literature, CM is most commonly diagnosed in children, whereas SM predominates in adults; consequently, the appearance of typical skin lesions in adults often leads to a suspicion of SM. However, CM must be distinguished from SM in adults, as the prognosis for the cutaneous form is more favourable in terms of both event-free survival and overall survival. Therefore, in all adult patients, it is essential to perform a detailed bone marrow examination to confirm or rule out SM and determine the prognosis. If this examination has not yet been performed and cutaneous symptoms of mastocytosis are present, a provisional diagnosis of mastocytosis in the skin (MIS) is applied. Patients should also be informed about possible diagnoses, their clinical significance, prognosis and treatment options. In patients with cutaneous mastocytosis, a scoring system such as the ECNM or Fuchs score should also be used to assess the likelihood of SM [15].

The diagnosis and classification of mastocytosis are based on established WHO criteria. The Tables below summarize the key diagnostic features and disease subtypes.

Symptomatic treatment. Systemic mastocytosis presents with a wide range of symptoms. These result from mediator release by activated mast cells and from tissue infiltration,

Table 1. WHO diagnostic criteria for systemic mastocytosis (2022) (adopted from [16])

Major criterion	Minor criteria
1) multifocal, dense mast cell infiltration (clusters of ≥ 15 mast cells) in bone marrow trepanobiopsy and/or biopsies of other organs (except skin).	1) atypical mast cells in bone marrow smears or spindle-shaped mast cells in infiltrates of these cells in a bone marrow or other organ biopsy (except skin), constitute $\geq 25\%$ of all mast cells. 2) presence of an activating point mutation in the KIT gene at codon 816 (most commonly D816V) or other critical regions of this gene in the bone marrow or other organ (except skin). 3) mast cells in bone marrow, blood or other organs (except skin) expressing CD2 and/or CD25 and/or CD30 (by immunophenotyping or immunohistochemistry). 4) serum tryptase levels >20 ng/ml (not applicable to patients who already have another myeloid neoplasm); this cut-off should be adjusted in patients with hereditary α -tryptasaemia.

To make a diagnosis, 1 major and 1 minor or 3 minor criteria must be met

Table 2. WHO classification of mastocytosis (2022)

Cutaneous mastocytosis (CM)	
Maculopapular CM (MPCM) monomorphic or polymorphic form	no B or C- findings *
Diffuse CM (DCM)	
Mastocytoma isolated or multilocalized	
Systemic mastocytosis (SM)	
bone marrow mastocytosis (BMM)	no B- and C-findings or skin involvement, tryptase <125 ng/ml, no dense infiltration of SM in extramedullary organs
indolent SM (ISM)	≤1 B-finding, no C-findings
smoldering SM (SSM)	≥2 B-findings, no C-findings
aggressive SM (ASM)	≥1 C-finding
SM-associated hematologic neoplasm (SM-AHN)	diagnosis of concomitant neoplasm of the haematopoietic system (myeloid or lymphoid)
mast cell leukemia (MCL)	chronic MCL: no symptoms acute MCL: ≥1 C-findings
Mast cell sarcoma (MCS)	

Well-differentiated systemic mastocytosis (WDSM) can occur in any of the SM subtypes and is characterised by round mast cells (usually CD30+, CD25-, CD2-) with numerous granules that usually infiltrate the marrow. In most cases, no mutation of the KIT gene at codon 816 is detected (WDSM).

* B ('burden of disease') findings include: >30% mast cells in bone marrow trepanobiopsy and/or serum tryptase concentration >200 ng/ml and/or D816V mutation of the KIT gene with a variant allele frequency ≥10% in bone marrow or blood leukocytes; features of myelodysplasia (discrete, i.e. in <10% of neutrophils, erythrocytes and megakaryocytes) and/or myeloproliferation (increased bone marrow cellularity with loss of fat cells and marked myelopoiesis, with possibly a shift in the percentage of blood granulocytes to the left and eosinophilia, and possibly leukocytosis with eosinophilia), but not fulfilling the diagnostic criteria for another disease; enlargement of the liver on palpation without ascites or other signs of liver damage, and/or enlargement of the spleen on palpation without hypersplenism or weight loss, and/or enlargement of the lymph nodes on palpation or imaging (>2 cm on ultrasound or CT).
C ('cytoreduction-requiring') findings include: neutropenia <1000/μl; anaemia (Hb <10 g/dl); thrombocytopenia <100,000/μl; ascites and increased liver enzymes with possible hepatic enlargement or cirrhosis with possible portal hypertension; enlargement of the spleen on physical examination and hypersplenism with possible weight loss or hypoalbuminaemia; impaired absorption with hypoalbuminaemia and possible weight loss; extensive osteolytic lesions (≥2 cm) and/or pathological fractures with possible bone pain.

which may lead to organ dysfunction. Management depends on the clinical presentation, symptom severity, and disease subtype. Current recommendations from the ECNM and NCCN support a stepwise, symptom-based approach. However, most of these recommendations rely on expert opinion and observational data rather than randomized trials. Anti-mediator therapy is the cornerstone of treatment in all forms of mastocytosis [18]. Histamine H1 receptor antagonists are used as first-line therapy for skin symptoms such as pruritus and erythema. Both second-generation (cetirizine, fexofenadine) and first-generation (hydroxyzine, ketotifen) agents are used. If the response is insufficient, anti-leukotriene drugs (montelukast, zafirlukast) may be added. In more severe cases, PUVA therapy can be considered. Acetylsalicylic acid may be used in selected patients, but caution is needed [19]. In practice, treatment is often individualized, as direct comparisons between available options are limited. Omalizumab, an anti-IgE monoclonal antibody, is increasingly used off-label in patients with severe disease. Available studies suggest it can reduce vasomotor and gastrointestinal symptoms, prevent anaphylaxis, and improve quality of life [20]. In addition, based on a systematic review that analysed data from two cohort studies and case series on a total of 69 patients, an effect on improving patients' quality of life was observed by effectively preventing anaphylaxis in 84%

of patients, and reducing mediator-dependent symptoms [21]. However, most data come from small cohorts and case series, which limits the strength of the evidence, and randomized trials are still needed. For gastrointestinal symptoms, histamine H2 receptor antagonists (ranitidine, famotidine, cimetidine) are commonly used. Proton pump inhibitors are considered second-line therapy. In selected cases, low-dose corticosteroids or cromoglycate may also be helpful [22]. Again, many of these approaches are based on clinical experience rather than strong evidence. Neurological and neuropsychiatric symptoms are also reported, which include headaches, anxiety, depression, and cognitive impairment. Their exact mechanism is not fully understood. Treatment is mainly symptomatic and may include antihistamines or cromoglycate. This remains an area where further research is needed. Patient education is a key part of management. Patients should be informed about triggers of mast cell activation and the increased risk of anaphylaxis. Proper training in the use of adrenaline autoinjectors is essential [23]. In cases of hypersensitivity to hymenopterous insect venoms, allergen immunotherapy with wasp and bee venom (VIT) should be considered [24]. In 20% of cases, osteopenia, osteoporosis, or fractures resulting from bone fragility complicating systemic mastocytosis, particularly ISM, are observed. Histamine released from mast cells is involved in the pathomechanism of secondary osteoporosis, which stimulates both osteoclasts and their precursors, and tumour necrosis factor TNF- α , interleukin (IL)-1 and IL-6 play a major role in promoting osteoclast activity and inhibiting osteoblasts. Bone involvement is a frequent complication, especially in indolent systemic mastocytosis. Osteopenia, osteoporosis, and fractures are commonly observed. Treatment includes bisphosphonates in patients with reduced bone density (T-score < -2). Denosumab can be used when bisphosphonates are not tolerated or contraindicated. Both options may reduce fracture risk and, in some cases, serum tryptase levels. In refractory cases, cytoreductive therapy may be required [15].

Cytoreductive treatment. For clinical forms with a severe course and serious prognosis, such as ASM, SM-AHN, MCL, it is advisable to include cytoreductive therapy usually with interferon-alpha (IFN- α), cladribine (2-chlorodeoxyadenosine) or polychemotherapy. Cytoreductive treatment is also used in patients with intense disease symptoms that respond poorly to standard symptomatic treatment and with contraindications to tyrosine kinase inhibitors [25]. In a study involving 47 patients receiving treatment with interferon alfa (with or without prednisone), an Objective Response Rate (ORR) of 60% and 45% was reported in the ASM and SM-AHN groups, respectively. The median duration of sustained response was 12 months (range 1–67 months). It was observed that cytopenias, flu-like symptoms and depression were the main side-effects of the therapy [26]. Furthermore, IFN- α remains the safest therapeutic option in pregnant patients [27].

In contrast, a retrospective Mayo Clinic study confirmed the therapeutic effect of cladribine in all forms of MS. In 22 patients with ISM, ASM AND SH-AHN, the ORR was 55%, with a median duration of response of 11 months (range 3–74 months) [28]. Another retrospective study that included 68 patients, including 36 with ISM and 32 with advanced MS treated with cladribine showed an ORR of 72%, with

50% in those with advanced mastocytosis (AdvSM). After a follow-up period of more than 10 years, the duration of response was 2.5 years (range 0.5–8.6 years) for ASM and 4.8 years (range 0.3–6.4 years) for SM-AHN. The most common adverse effects included myelosuppression (grade 3–4) and opportunistic infections [29].

Kinase inhibitors in mastocytosis. New options for the targeted therapy of mastocytosis have been made possible by the introduction of tyrosine kinase inhibitors in recent years, particularly in cases where antihistamines, corticosteroids, and mast cell stabilisers have not been effective. The downstream signalling that promotes mast cell activation, proliferation, and survival may be disrupted by these inhibitors [30]. The impact of JAK inhibitors, such as fedratinib and gandotinib, on human MC with KIT D816V mutation and human primary cord blood-derived MC was investigated in one of the most recent studies. These JAK inhibitors caused apoptosis, decreased proliferation, and decreased viability in MC lines that were positive for KIT D816V. In MC generated from primary cord blood, fedratinib also caused apoptosis. Furthermore, fedratinib and gandotinib were shown to amplify the cytotoxic and anti-proliferative actions of tyrosine kinase inhibitors. This may imply that these inhibitors are a new method of treating mastocytosis [31]. With a regular dosage schedule and limited penetration into the central nervous system (CNS), elenestib (BLU-263) is a strong and specific small-molecule inhibitor of KITD816V. In a phase 1 trial, the safety and tolerability profiles of the agent were favourable [25]. Patients with ISM are part of the ongoing randomized double-blind phase 2/3 HARBOR study (NCT04910685) [32]. When compared to placebo, patients who received elenestib at dosages of 25 mg, 50 mg, and 100 mg demonstrated mean percentage reductions of -15.4%, -50.9%, and -68.4% in tryptase, respectively, and KITD816V VAF (-37.5%, -70.3%, and -77.0% vs -2.5%, respectively) [33]. While bezuclastinib avoids closely related kinases like PDGFR α , PDGFR β , and CSF1R, which would have clinical consequences if blocked, it is a very selective and powerful inhibitor of mutant KIT, including KIT D816V and mutations in exons 9, 11, 17, and 18 [30]. In preclinical trials, bezuclastinib only weakly crossed the blood-brain barrier and did not cause toxicities to the central nervous system [34].

The APEX (NCT04996875) trial is a large, multi-centre phase II open label study that is now evaluating bezuclastinib in patients with AdvSM. Serum tryptase, KIT-D816V VAF, and bone marrow mast cell burden were all reduced by at least 50% in over 93% of patients. Bleeding and cognitive impairment were not adverse consequences [35]. The most frequent adverse events were peripheral oedema (19%), neutropenia (25%), taste alteration (25%), and hair whitening (25%). Additionally, information from the SUMMIT trial (NCT05186753), a phase 2 randomized, double-blind, placebo-controlled study in NonAdvSM patients, has been provided. The treatment has been linked to quick symptom relief (49% mean improvement in quality-of-life (McQoL) at week 12) [36]. These findings support further investigation of bezuclastinib as a targeted therapeutic agent for patients with advanced SM, particularly those with limited response or intolerance to existing treatment options such as midostaurin or avapritinib.

The most recent and highly targeted TKI approved for advanced systemic mastocytosis is avapritinib, a potent inhibitor that selectively binds to the KIT D816V mutant

receptor. Avapritinib's effectiveness in treating patients with advanced systemic mastocytosis was investigated in a clinical trial. In the great majority of patients, avapritinib decreased spleen volume, serum tryptase, KIT D816V VAF in peripheral blood, and bone marrow mast cell infiltration. KIT D816V VAF in blood was reduced by at least 50% in two-thirds of avapritinib-treated patients, with nearly one-fourth of them reaching levels below the detection limit. Avapritinib treatment was linked to quick, profound, and long-lasting effects, such as a significant decrease in the disease burden in SM [37]. Avapritinib excelled a placebo in the 24-week blinded phase of the PIONEER study when it came to alleviating symptoms in patients with moderate to severe indolent systemic mastocytosis. From baseline to week 24, 54% patients in the avapritinib group, compared with 0% in the placebo group, had a $\geq 50\%$ reduction in serum tryptase level. The 68% in the avapritinib group had a $\geq 50\%$ reduction in KIT D816V VAF in peripheral blood compared with only 6% of patients in the placebo group. Furthermore, 25% of avapritinib-treated patients had a $\geq 50\%$ reduction in TSS compared with 10% of placebo-treated patients. From baseline to week 24, 53% of avapritinib-treated patients had a $\geq 50\%$ reduction in bone marrow mast-cell burden compared with 23% of placebo-treated patients [38].

Before avapritinib, midostaurin was the first TKI approved for the treatment of advanced systemic mastocytosis. As a multi-kinase inhibitor, midostaurin targets not only KIT D816V but also other signalling pathways, in contrast to avapritinib. Midostaurin has shown significant clinical benefit in the treatment of advanced systemic mastocytosis (ASM), including aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematologic neoplasm (SM-AHN), and mast cell leukemia (MCL). Clinically, it has been demonstrated to improve survival and decrease mast cell infiltration in tissues, despite being less selective. It is still a highly effective therapy option, especially in situations where avapritinib is unavailable. In 116 patients with advanced SM, Gotlib et al. (2016) conducted a pivotal open-label, multi-centre, phase II research to assess the safety and effectiveness of midostaurin. Responses from all advanced SM subtypes were seen in the trial, which showed an overall response rate of 60%. Serum tryptase levels and mast cell burden, were significantly decreased by midostaurin, which also improved organ function and mediator-related symptoms, such flushing, gastrointestinal issues, and anaphylaxis [39].

Key characteristics of selected tyrosine kinase inhibitors are summarized in Table 3.

Treatment with antibodies. Treatment of systemic mastocytosis refractory to treatment and at an advanced stage may be based on the use of antibody-drug conjugates. One of the preparations used is gemtuzumab ozogamycin (GO) combined with polychemotherapy. It has the desired effect in a disease variant in which either the (sub)clone is not dominant or the c-KIT D816V mutation is absent, but CD33 expression is present [40]. Gemtuzumab ozogamycin has high affinity for the CD33 receptor. Then binding to CD33 is transported from the endosome to the lysosome after ADC internalisation [41]. A free calicheamicin derivative is then formed and translocated to the cell nucleus, which causes cell cycle arrest and apoptosis [42]. Another reference for the treatment of systemic mastocytosis may be sialic acid-binding immunoglobulin-like lectin (Siglec-8),

Table 3. Kinase inhibitors in mastocytosis

Drug	Target	Indication	Key findings	Limitations
Avapritinib	KIT D816V (highly selective)	AdvSM, ISM (studies ongoing)	Rapid and deep responses; ↓ tryptase, ↓ KIT VAF, ↓ mast cell burden; symptom improvement (PIONEER)	CNS adverse effects possible; cost/access
Midostaurin	Multikinase (incl. KIT D816V)	AdvSM (ASM, SM-AHN, MCL)	ORR ~60%; ↓ mast cell burden; improved survival and symptoms	Less selective; broader toxicity profile
Bezuclastinib	Selective KIT (incl. D816V)	AdvSM, Non-AdvSM (trials)	≥50% reduction in tryptase and KIT VAF in >90% patients (APEX); QoL improvement (SUMMIT)	Still under investigation; phase II data
Elenestinib (BLU-263)	KIT D816V (selective)	ISM (HARBOR trial)	Dose-dependent ↓ tryptase and KIT VAF; good tolerability	Early-phase data
JAK inhibitors (fedratinib, gandotinib)	JAK pathways	Preclinical	Induce apoptosis; enhance TKI effects	No strong clinical data yet

which is an inhibitory receptor selectively expressed on human interstitial cells, eosinophils and in basophils (to a lesser extent) [43]. The combination of the monoclonal antibody with Siglec-8 induces apoptosis of eosinophils and generally inhibits interstitial cell activation, including two modes of activation-dependent and IgE-independent [44]. Lirontelimab is the first humanised non-fucosylated IgG1 monoclonal antibody in its class directed against Siglec-8. On the basis of preclinical studies, lirontelimab has been shown, to be a highly specific and selective antibody against Siglec-8, to inhibit interstitial cell activation and to reduce inflammatory mediators and activation markers – studies conducted on bone marrow cells collected from patients with systemic mastocytosis. Under the influence of lirontelimab, eosinophils are rapidly cleared by both direct induction and antibody-dependent induction of eosinophil cytotoxicity [45]. In the first clinical trial conducted on a small group of patients aged 18–65 years diagnosed with indolent systemic mastocytosis, the effect of lirontelimab was evaluated in humans. Following an appropriate treatment regimen, symptoms associated with severe systemic mastocytosis and laboratory parameters were assessed. The greatest improvements occurred in gastrointestinal, skin, nervous system and musculoskeletal symptoms. There was also a significant decrease in eosinophilia in laboratory tests. However, no changes in urinary histamine metabolites were observed, but the significant improvement on the side of disease symptoms is a promising indicator of inhibition of interstitial cell activation. In addition, the side-effects reported by patients were relatively mild and were well tolerated [46]. As the available knowledge on this preparation is limited, it requires further study.

In the case of brentuximab vedotin, opinions are conflicting regarding its efficacy. The number of studies is also limited, resulting in a lack of options for use in the treatment of systemic mastocytosis. Brentuximab vedotin is an antibody-drug conjugate consisting of the chimeric immunoglobulin G1 antibody cAC10 and monomethylauristatin E (MMAE) [47]. Studies on this therapy have been performed on very small groups of patients. The study described on a group of four patients suggests a positive effect of brentuximab vedotin on the course of the disease, and indicates that side-effects can be controlled by modifying the dose [48]. In contrast, another study (in 10 patients) showed insufficient efficacy with this product, making this therapy unsuitable for use in the severe systemic mastocytosis population. However, this study confirms the good tolerability of the drug and the relatively minor side effects [49]. In conclusion, the greatest hopes for the efficacy of the use of immune therapy

in severe systemic mastocytosis are shown by gemtuzumab ozogamycin (GO) combined with polychemotherapy and lirontelimab, but this one, due to the limited knowledge available, requires additional studies.

Allogeneic haematopoietic stem cell transplantation (allo-HSCT). The aggressive form of systemic mastocytosis can be treated with allogeneic haematopoietic stem cell transplantation (allo-HSCT). This is the treatment of choice for advanced systemic mastocytosis, and is used in patients who have not responded to treatment. In the case of resistant or rapidly progressive advanced SM, treatment regimens used in high-risk acute myeloid leukemia are recommended. This is the only available method that allows for a complete cure of the disease. However, the success of this therapy depends on many factors, the most important of which is the coexistence of other haematologic malignancies, such as associated haematologic neoplasms (AHN) or mast cell leukemia (MCL) [40]. There is a lack of studies confirming the impact of maintenance therapy with a KIT inhibitor on long-term survival. However, it is recommended to administer midostaurin to patients eligible for allo-HSCT at the start of conditioning, and then resume treatment 30 days post-transplant [50]. Due to the limited data available, determining the success of this therapy is challenging. A significantly larger body of research confirms the efficacy of allo-HSCT in the course of AML (acute myeloid leukemia) [51,52]. There are isolated case reports regarding the treatment of advanced mastocytosis, which precludes a thorough analysis of this therapy's efficacy.

CONCLUSIONS

Management should be tailored to disease subtype and symptom burden. In cutaneous and indolent systemic mastocytosis, treatment focuses on mediator-related symptom control and prevention of anaphylaxis. In contrast, advanced systemic mastocytosis requires disease-modifying therapy. Tyrosine kinase inhibitors targeting KIT have demonstrated meaningful reductions in mast cell burden, serum tryptase levels, organ damage, and symptom severity, translating into improved clinical outcomes. Cytoreductive agents, such as interferon- α or cladribin, remain relevant options in selected patients, while allogeneic haematopoietic stem cell transplantation should be considered in eligible individuals with aggressive disease or treatment failure.

Future priorities include optimization of therapeutic sequencing, identification of predictors of response

and resistance, and validation of emerging targeted and immunotherapeutic strategies in prospective clinical trials. A precision medicine approach integrating clinical features with molecular profiling is critical to further improving survival and quality of life in patients with mastocytosis. Nevertheless, there is a need to further develop research in this area.

REFERENCES

- Valent P, Akin C, Sperr WR, et al. New insights into the pathogenesis of mastocytosis: emerging concepts in diagnosis and therapy. *Annu Rev Pathol.* 2023;18:361–386. <https://doi.org/10.1146/annurev-pathmechdis-031521-042618>.
- González-López O, Muñoz-González JI, Orfao A, et al. Comprehensive analysis of acquired genetic variants and their prognostic impact in systemic mastocytosis. *Cancers (Basel).* 2022;14(10):2487. <https://doi.org/10.3390/cancers14102487>
- Swarnkar B, Sarkar R. Childhood cutaneous mastocytosis: revisited. *Indian J Dermatol.* 2023;68(1):121. https://doi.org/10.4103/ijid.ijd_264_22
- Bergström A, Hägglund H, Berglund A, et al. Epidemiology of mastocytosis: a population-based study (Sweden). *Acta Oncol.* 2024;63:44–50. <https://doi.org/10.2340/1651-226X.2024.31406>
- Orphanet: Systemic mastocytosis. <https://www.orpha.net/en/disease/detail/2467> (access: 2026.02.24).
- Cilloni D, Maffeo B, Savi A, et al. Detection of KIT mutations in systemic mastocytosis: how, when, and why. *Int J Mol Sci.* 2024;25(20):10885. <https://doi.org/10.3390/ijms252010885>.
- Kristensen T, Vestergaard H, Møller MB. Improved detection of the KIT D816V mutation in patients with systemic mastocytosis using a quantitative and highly sensitive real-time qPCR assay. *J Mol Diagn.* 2011;13(2):180–188. <https://doi.org/10.1016/j.jmoldx.2010.10.004>.
- Rigo R, Chelbi R, Agopian J, et al. TET2 regulates immune tolerance in chronically activated mast cells. *JCI Insight.* 2022;7(7):e154191. <https://doi.org/10.1172/jci.insight.154191>.
- Elieh Ali Komi D, Wöhrl S, Bielory L. Mast cell biology at molecular level: a comprehensive review. *Clin Rev Allergy Immunol.* 2020;58(3):342–365. <https://doi.org/10.1007/s12016-019-08769-2>
- Valent P, Akin C, Hartmann K, et al. Mast cells as a unique hematopoietic lineage and cell system: from Paul Ehrlich's visions to precision medicine concepts. *Theranostics.* 2020;10(23):10743–10768. <https://doi.org/10.7150/tno.46719>
- Dahlin JS, Ekoff M, Grootens J, et al. KIT signaling is dispensable for human mast cell progenitor development. *Blood.* 2017;130(16):1785–1794. <https://doi.org/10.1182/blood-2017-03-773374>
- Olivera A, Beaven MA, Metcalfe DD. Mast cells signal their importance in health and disease. *J Allergy Clin Immunol.* 2018;142(2):381–393. <https://doi.org/10.1016/j.jaci.2018.01.034>
- McLeod JJA, Baker BN, Ryan JJ. Mast cell production and response to IL-4 and IL-13. *Cytokine.* 2015;75(1):57–61. <https://doi.org/10.1016/j.cyto.2015.05.019>
- Theoharides TC. The impact of psychological stress on mast cells. *Ann Allergy Asthma Immunol.* 2020;125(4):388–392. <https://doi.org/10.1016/j.anai.2020.07.007>
- Gotlib J, Gerds AT, Abdelmessieh P, et al. NCCN Guidelines® Insights: Systemic mastocytosis, version 3.2024. *J Natl Compr Canc Netw.* 2024;22(2):e240030. <https://doi.org/10.6004/jnccn.2024.0030>
- Arber DA, Orazi A, Hasserjian R, et al. International consensus classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. *Blood.* 2022;140(11):1200–1228.
- 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(7):1703–1719. <https://doi.org/10.1038/s41375-022-01613-1>
- Dea K, Ryan T, Wlodarski S. Mastocytosis: from a molecular point of view. *Clin Rev Allergy Immunol.* 2018;54(3):397–411. <https://doi.org/10.1007/s12016-017-8619-2>
- Pardanani A. Systemic mastocytosis in adults: 2023 update on diagnosis, risk stratification and management. *Am J Hematol.* 2023;98(7):1097–1116. <https://doi.org/10.1002/ajh.26962>
- Lemal R, Fouquet G, Terriou L, et al. Omalizumab therapy for mast cell-mediator symptoms in patients with ISM, CM, MMAS, and MCAS. *J Allergy Clin Immunol Pract.* 2019;7(7):2387–2395.e3. <https://doi.org/10.1016/j.jaip.2019.03.039>
- Jendoubi F, Gaudenzio N, Gallini A, et al. Omalizumab in the treatment of adult patients with mastocytosis: a systematic review. *Clin Exp Allergy.* 2020;50(6):654–661. <https://doi.org/10.1111/cea.13592>
- Zanelli M, Pizzi M, Sanguedolce F, et al. Gastrointestinal manifestations in systemic mastocytosis: the need of a multidisciplinary approach. *Cancers (Basel).* 2021;13(13):3316. <https://doi.org/10.3390/cancers13133316>
- Gulen T. Management of mediator symptoms, allergy, and anaphylaxis in mastocytosis. *Immunol Allergy Clin North Am.* 2023;43(4):681–698. <https://doi.org/10.1016/j.iac.2023.04.010>
- Nittner-Marszalska M. Venom immunotherapy. *Alergol Pol.* 2018;5(2):85–93. <https://doi.org/10.5114/pja.2018.76677>
- Tremblay D, Wagner NE, Mascarenhas J. Management of advanced systemic mastocytosis: clinical challenges. *J Blood Med.* 2024;15:421–433. <https://doi.org/10.2147/JBM.S366367>
- Lee HJ. Recent advances in diagnosis and therapy in systemic mastocytosis. *Blood Res.* 2023;58(S1):96–108. <https://doi.org/10.5045/br.2023.2023024>
- Ferrari J, Benvenuti P, Bono E, et al. Mastocytosis: fertility and pregnancy management in a rare disease. *Front Oncol.* 2022;12:874178. <https://doi.org/10.3389/fonc.2022.874178>
- Lim KH, Pardanani A, Butterfield JH, et al. Cytoreductive therapy in 108 adults with systemic mastocytosis: outcome analysis and response prediction. *Am J Hematol.* 2009;84(12):790–794. <https://doi.org/10.1002/ajh.21561>
- Barete S, Lortholary O, Damaj G, et al. Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. *Blood.* 2015;126(8):1009–1016. <https://doi.org/10.1182/blood-2014-12-614743>
- Chifotides HT, Bose P. SOHO state of the art update and next questions: current and emerging therapies for systemic mastocytosis. *Clin Lymphoma Myeloma Leuk.* 2025;25(1):1–12. <https://doi.org/10.1016/j.clml.2024.06.005>
- Makeeva A, Stivala S, Ratti E, et al. Fedratinib and ganadotinib induce apoptosis and enhance the efficacy of tyrosine kinase inhibitors in human mast cells. *Am J Cancer Res.* 2025;15(1):84–98.
- Castells M, Scherber R, Bhavsar V, et al. HARBOR: a phase 2/3 study of BLU-263 in patients with indolent systemic mastocytosis and monoclonal mast cell activation syndrome. *HemaSphere.* 2022;6(Suppl):907–908. <https://doi.org/10.1097/01.HS9.0000846936.51452.f2>
- Tashi T, Hermine O, Castells M, et al. Elenestininib, a next-generation KIT D816V inhibitor, reduces mast cell burden and improves symptoms in indolent systemic mastocytosis. *Blood.* 2023;142(Suppl 1):76. <https://doi.org/10.1182/blood-2023-188904>
- Guarnieri A, Chicarelli M, Cable L, et al. Preclinical data with KIT D816V inhibitor bezuclastinib demonstrates high selectivity and minimal brain penetration. *Blood.* 2021;138(Suppl 1):4595. <https://doi.org/10.1182/blood-2021-152770>
- Gotlib J, George TI, Deininger MW, et al. A phase 2 study of bezuclastinib in adult patients with advanced systemic mastocytosis. *Blood.* 2021;138(Suppl 1):3636. <https://doi.org/10.1182/blood-2021-145928>
- Reiter A. SUMMIT part 2 trial in progress: a global, randomized study in patients with non-advanced systemic mastocytosis. Presented at: EHA Congress; 2024. <https://library.ehaweb.org/eha/2024/eha2024congress/421658/andreas.reiter.summit.part.2.trial.in.progress.a.global.randomized.html> (access: 2025.04.23).
- Reiter A, Schwaab J, DeAngelo DJ, et al. Efficacy and safety of avapritinib in previously treated patients with advanced systemic mastocytosis. *Blood Adv.* 2022;6(21):5750–5762. <https://doi.org/10.1182/bloodadvances.2022007539>
- Gotlib J, Castells M, Elberink HO, et al. Avapritinib versus placebo in indolent systemic mastocytosis. *NEJM Evid.* 2023;2(6):EVIDoA2200339. <https://doi.org/10.1056/EVIDoA2200339>
- Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. *N Engl J Med.* 2016;374(26):2530–2541. <https://doi.org/10.1056/NEJMoa1513098>
- Hus M, Szudy-Szczyrek A, Helbig G, et al. Diagnosis and treatment of systemic mastocytosis—experts' statement. *Hematol Clin Pract.* 2020;11(2):61–72. <https://doi.org/10.5603/Hem.2020.0008>
- Jedema I, Barge RM, van der Velden VH, et al. Internalization and cell cycle-dependent killing of leukemic cells by gemtuzumab ozogamicin. *Leukemia.* 2004;18(2):316–325. <https://doi.org/10.1038/sj.leu.2403205>
- van der Velden VH, te Marvelde JG, Hoogeveen PG, et al. Targeting of the CD33-calicheamicin immunoconjugate Mylotarg in acute myeloid leukemia. *Blood.* 2001;97(10):3197–3204. <https://doi.org/10.1182/blood.v97.10.3197>

43. Legrand F, Cao Y, Wechsler JB, et al. Siglec-8 in patients with eosinophilic disorders: receptor expression and targeting using chimeric antibodies. *J Allergy Clin Immunol*. 2019;143(6):2227–2237.e10. <https://doi.org/10.1016/j.jaci.2018.10.066>
44. Bochner BS, O'Sullivan JA, Chang AT, et al. Siglecs in allergy and asthma. *Mol Aspects Med*. 2023;90:101104. <https://doi.org/10.1016/j.mam.2022.101104>
45. Schanin J, Gebremeskel S, Korver W, et al. A monoclonal antibody to Siglec-8 suppresses non-allergic airway inflammation. *Mucosal Immunol*. 2021;14(2):366–376. <https://doi.org/10.1038/s41385-020-00336-9>
46. Siebenhaar F, Altrichter S, Bonnekoh H, et al. Safety and efficacy of lircatelimab in patients with refractory indolent systemic mastocytosis. *Br J Dermatol*. 2023;189(5):511–519. <https://doi.org/10.1093/bjd/ljad191>
47. Blatt K, Cerny-Reiterer S, Schwaab J, et al. Identification of CD30 as a novel therapeutic target in systemic mastocytosis. *Blood*. 2015;126(26):2832–2841. <https://doi.org/10.1182/blood-2015-03-637728>
48. Borate U, Mehta A, Reddy V, et al. Treatment of CD30-positive systemic mastocytosis with brentuximab vedotin. *Leuk Res*. 2016;44:25–31. <https://doi.org/10.1016/j.leukres.2016.02.010>
49. Gotlib J, Baird JH, George TI, et al. A phase 2 study of brentuximab vedotin in patients with CD30-positive advanced systemic mastocytosis. *Blood Adv*. 2019;3(15):2264–2271. <https://doi.org/10.1182/bloodadvances.2019000152>
50. Ustun C, Gotlib J, Popat U, et al. Consensus opinion on allogeneic hematopoietic cell transplantation in advanced systemic mastocytosis. *Biol Blood Marrow Transplant*. 2016;22(8):1348–1356. <https://doi.org/10.1016/j.bbmt.2016.04.018>
51. Ustun C, Reiter A, Scott BL, et al. Hematopoietic stem-cell transplantation for advanced systemic mastocytosis. *J Clin Oncol*. 2014;32(29):3264–3274. <https://doi.org/10.1200/JCO.2014.55.2018>
52. Webster JA, Luznik L, Gojo I. Treatment of AML relapse after allo-HCT. *Front Oncol*. 2021;11:812207. <https://doi.org/10.3389/fonc.2021.812207>