doi.org/10.58931/cht.2024.3149

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Systemic Mastocytosis: Diagnosis and Management in 2024

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Abstract

Mastocytosis is a group of clonal disorders characterized by an accumulation of neoplastic mast cells (MCs) in one or more organ systems. The clinical presentation of mastocytosis is heterogenous as are the clinical outcomes. For example, some variants are associated with near normal life expectancy, while others are amongst the most aggressive known malignancies. Mastocytosis can occur in both pediatric and adult populations and can be classified into three major groups: systemic mastocytosis (SM), cutaneous mastocytosis (CM), and localized mast cell sarcoma. This review will focus on SM in adults with the aim of providing a general overview of the **(1)** pathophysiology, **(2)** diagnostic approach, and **(3)** current treatment landscape in Canada.

Epidemiology

SM is a rare neoplasm. The incidence and prevalence of SM are poorly characterized due to its rarity, but estimated at 1/100 000 and 1/10 000, respectively.[1,2] While evidence suggests that SM has a higher prevalence in women, advanced disease appears to be more common in men.[2,3] The mean age at diagnosis occurs in the 5th to 7th decade of life and the median time to diagnosis from symptom onset is estimated to be approximately 3 years.[3]

Pathophysiology of Systemic Mastocytosis

Human MCs originate from CD34^{+} pluripotent progenitor cells in the bone marrow.[4] Mature MCs in their normal state have a well described role as effector cells in immediate-type hypersensitivity reactions.[5–7] A critical part of the differentiation, growth, and survival of MCs is the interaction of stem cell factor (SCF) with KIT, a tyrosine-kinase receptor located on the surface of MCs. Mutations in the *KIT* gene are present in approximately >90% of patients with SM and by far the most common mutation among them is the *KIT* p.D816V mutation. This mutation induces a constitutive SCF-independent hyperactivation state of the KIT receptor, which contributes to

an over production of MCs, an amplification of MC mediator release, and the accumulation of MCs in organs such as the bone marrow, skin, liver, spleen, lymph nodes, and gastrointestinal (GI) tract.[8–11]

Clinical Presentation of Systemic Mastocytosis

Allergy and Mediator Symptoms

Many patients with SM, especially those with non-advanced disease, often present with symptoms related to excessive MC activation. The release of mediators from MCs affects multiple organs, and patients can exhibit a variety of symptoms including cutaneous (e.g., flushing, pruritus, hives), cardiovascular (e.g., dizziness, syncope), GI (e.g., diarrhea, nausea, vomiting, abdominal pain, gastroesophageal reflux disease), musculoskeletal (e.g., bone pain), and neuropsychiatric symptoms (e.g., brain fog, anxiety, depression), fatigue, and anaphylaxis. Common triggers for MC activation include exercise, changes in temperature, physical and emotional stress, food, alcohol, medications (e.g., nonsteroidal anti-inflammatory agents, anesthetic agents, opioids), radiocontrast agents, invasive procedures, and venoms.[7] In SM, the rate of anaphylaxis is significantly higher than that of the general population, and is estimated to occur in approximately 20–50% of adult patients with SM.[12,13] An important trigger to be aware of is hymenoptera venom (e.g. yellowjacket wasp, paper wasp, honeybee, fire ant). Anaphylaxis from hymenoptera venom is estimated to account for up to one third of all cases of anaphylaxis, is a risk factor for severe recurrent anaphylaxis, and is often the presenting symptom in patients with indolent SM.[14–18]

Bone

Bone abnormalities are common clinical features in patients with SM. Osteoporosis/osteopenia occurs in approximately 20–40% of patients with indolent SM and the prevalence of these bone abnormalities tends to be higher in men. Patients can also present with osteosclerosis, which tends to be more common in advanced stages of the disease, as well as lytic bone lesions in the axial and appendicular skeleton that can mimic skeletal metastasis.[19–23]

Organ Infiltration

Infiltration of MCs into the skin is a common finding in SM, especially in non-advanced stages of the disease.[24] The most common skin manifestation of SM is maculopapular CM (previously referred to as urticaria pigmentosa), which is characterized by small, round, brown/red monomorphic lesions and Darier's sign is usually evident in these cases.[24] In adult-onset mastocytosis in the skin, the likelihood of having SM is extremely high (up to 97% in some studies).[25] Patients with SM can present with lymphadenopathy and splenomegaly due to MC and/or eosinophil infiltration along with possible extramedullary hematopoiesis. Progressive lymphadenopathy and significant splenomegaly are more commonly observed in advanced stages of the disease.[7] MC infiltration of the liver is common and can occur with liver dysfunction, ascites, and portal hypertension, all of which reflect advanced SM. Patients with SM can present with malabsorption and weight loss, which is also suggestive of advanced stages of the disease.[7]

Establishing the Diagnosis

Initial Workup:

International guidelines recommend that patients be referred to centres with experience in the diagnosis and management of SM.[26–28] The work up for SM includes a thorough history and physical exam, a complete blood count with differential and smear, a comprehensive metabolic panel, liver function tests, albumin, basal serum tryptase level, and imaging to evaluate for hepatosplenomegaly, lymphadenopathy, ascites and lytic bone lesions. To evaluate for biochemical evidence of MC activation, a referral to an experienced allergist should be initiated. SM is a histopathologic diagnosis and requires a biopsy of the involved tissues, and bone marrow is the gold standard for this purpose. In general, clinicians should have a high index of suspicion for SM in those with **(1)** symptoms compatible with MC activation, **(2)** an elevated basal serum tryptase level, **(3)** biopsy-proven adult onset mastocytosis in the skin, and/or **(4)** unexplained bone findings. In addition, the histopathologic analysis should include a myeloid next-generation sequencing panel that includes genes such as *SRSF2, ASXL1, RUNX1*, mast cell immunophenotyping by immunohistochemistry and/or flow cytometry, and cytogenetics. In the presence of eosinophilia

and bone marrow MC proliferation, screening for the known tyrosine kinase gene fusions associated with myeloid or lymphoid neoplasms with eosinophilia (e.g. *FIP1L1-PDGFRA*) should be performed.[29,30]

Diagnostic Criteria

The World Health Organization (WHO)[29,31] and International Consensus Criteria (ICC)[30] are two classification systems used to establish the diagnosis of SM. The criteria are very similar but not entirely aligned. (nuances are summarized in the NCCN guideline[28] and Pardanani et al.[27]) The main histopathologic feature used by both classification systems is the major criterion of multifocal dense aggregates (i.e. 15 or more MCs in aggregates) of MCs in the bone marrow or other extracutaneous tissue. Minor criteria include >25% of MCs with atypical morphology, any ligand-independent activating *KIT* mutation* (e.g. most commonly the *KIT* D816V mutation), an aberrant MC immunophenotype detected by flow cytometry or immunohistochemistry, and a baseline serum tryptase value of >20 ng/mL** (**Table 1**). The WHO requires 1 major and 1 minor criterion, or at least 3 minor criteria, and the ICC requires 1 major criterion or at least 3 minor criteria.[29,30]

*The prevalence of *KIT* p.D816V mutations varies on the disease subtype (typical ISM >90%, SSM >90%, SM-AHN, >90%, ASM >80%, MCL <70%)

**In cases of SM-AHN, an elevated tryptase does not count as a SM minor criterion. The WHO states that basal serum tryptase level should be adjusted in case of hereditary alpha-tryptasaemia.

Staging

After the diagnosis of SM is established, it is important to then classify SM into specific subtypes (also known as variants) as this is important for understanding natural history and for planning treatment. This process can be confusing, which is further compounded by the subtle differences between the ICC and WHO criteria, which are summarized in **Table 1**. SM can be broadly divided into two major categories: non advanced SM and advanced SM. Non advanced SM includes three subtypes: bone marrow mastocytosis (BMM), indolent SM (ISM), and smouldering SM (SSM). The hallmark of non-advanced SM is that there is no significant end organ damage. Advanced SM also includes three subtypes: aggressive SM (ASM), mast cell leukemia (MCL), and SM with associated hematological neoplasm (SM-AHN[a]). The criteria used to classify all three indolent subtypes and the ASM subtype are the "B" and "C" findings (**Table 2**). The diagnosis of MCL requires the presence of at least 20% mast cells in bone marrow aspirate smears. The diagnosis of SM-AHN requires diagnostic criteria for both **(1)** SM and **(2)** another hematologic (myeloid or rarely lymphoid) neoplasm to be simultaneously fulfilled. Common AHNs that co-exist with SM are chronic myelomonocytic leukemia, myelodysplastic syndrome, myeloproliferative neoplasms, chronic eosinophilic leukemia, and acute myeloid leukemia.

Treatment

Mediator Symptoms, Anaphylaxis and Bone Health

Multidisciplinary collaboration, especially with allergists, is necessary to optimize patient care. MC activation symptoms greatly affect patients' quality of life and are managed with anti-mediator therapies such as antihistamines, mast cell stabilizers, and leukotriene receptor antagonists. Counselling on trigger avoidance is crucial, especially with strategies to avoid insect bites and peri-procedural optimization.[28] It is recommended that all patients obtain a medical alert bracelet and/or wallet card, and must always carry two auto injectors of epinephrine with them at all times. All patients who have experienced anaphylaxis due to hymenoptera venom must be assessed by an allergist for venom immunotherapy and/or for omalizumab therapy for other severe allergic issues.[28,32,33] Because of the risk of excessive bone loss, serial bone mineral density scans are an important part of management and bisphosphonates with antihistamines are typically used as front-line therapies.[28]

Cytoreduction

Cytoreduction is typically indicated for those with end organ damage or with severe and refractory symptoms.[26–28] Cytoreductive options include midostaurin, avapritinib, cladribine, peginterferon alfa-2a, and imatinib. Most international guidelines recommend enrolment in a clinical trial, midostaurin or avapritinib as front-line therapies for advanced SM, as well as cladribine when rapid debulking is required.[26–28]

All variants must first meet SM diagnostic criteria
Bone marrow mastocytosis[a]
• SM established from bone marrow and no B findings, C findings, AHN or MCL
• No skin involvement
• Basal serum tryptase below 125 ng/mL
Indolent SM
• 0-1 B finding(s)
• No C findings, AHN or MCL
Smoldering SM
• ≥ 2 B findings
• No C findings, AHN or MCL
Aggressive SM
• ≥ 1 C finding
• No AHN or MCL
Systemic mastocytosis with Associated Hematological Neoplasm[b]
• Meets SM diagnostic criteria and diagnostic criteria for second hematological neoplasm (usually a myeloid neoplasm)
Mast Cell Leukemia
• Bone marrow aspirate smears ≥ 20% MC[c]

Table 1. Criteria for systemic mastocytosis variants; *courtesy of Stephanie Lee, MD*.

a) In the 2022 WHO classification, BMM is a separate category from ISM. In the 2022 ICC classification, BMM is a subvariant of ISM.[29]

b) In the 2022 ICC classification, this variant is named SM with an associated myeloid neoplasm (AMN) because overwhelmingly the concurrent neoplasms is myeloid origin.

c) The 2022 ICC states that MCs must be atypical immature cells, which include promastocytes, metachromatic blast-like cells, or highly pleomorphic mast cells. The ICC states in the presence of an inadequate bone marrow aspirate smear, MCL may be diagnosed by a diffuse, dense infiltration of atypical immature mast cells on bone marrow biopsy.[30]

B findings reflect the disease burden but without organ dysfunction and C findings reflect disease burden with organ dysfunction.
B findings
2022 WHO
• >30% mast cells on bone marrow biopsy and serum total tryptase >200 ng/mL
• Signs of dysplasia or myeloproliferation in non-mast cell lineage, but criteria not met for a WHO AHN, with normal or only slightly abnormal blood counts
• Hepatomegaly without impaired liver function, palpable splenomegaly without hypersplenism and/or lymphadenopathy (palpation or imaging)
• KIT D816V variant allele frequency ≥10%
2022 ICC
• >30% of bone marrow cellularity by mast cells and serum total tryptase >200 ng/mL
• Cytopenia but not meeting criteria for C-findings or -cytosis. Reactive causes are excluded and criteria for myeloid neoplasms are not met.
• Hepatomegaly without impaired liver function, palpable splenomegaly without hypersplenism and/or lymphadenopathy >1 cm (palpation or imaging)
C findings
• Bone marrow dysfunction due to neoplastic mast cell infiltration defined as ≥1 cytopenia: absolute neutrophil count <1.0 × 10^9/L, hemoglobin <100 g/L, and/or platelet count <100 × 10^9/L
• Palpable splenomegaly with hypersplenism
• Osteolytic lesion ≥2 cm
• Palpable hepatomegaly with impairment of liver function, and/or ascites, and/or portal hypertension
• Malabsorption with hypoalbuminemia +/- weight loss

Table 2. B- and C- Findings Criteria; *courtesy of Stephanie Lee, MD.*

Midostaurin is an oral multikinase inhibitor that has been approved for the treatment of advanced SM in Canada, the United States, and Europe. Two pivotal clinical trials have demonstrated the effectiveness of midostaurin in treating SM. The overall response rate (ORR) was approximately 60–69%, with median progression-free survival (PFS) and overall survival (OS) of 14 months and 29 months, respectively. All subvariants of advanced SM responded to the treatment, the patients reported an improved quality of life, and the main adverse events were GI toxicity and myelosuppression.[34,35] Unfortunately, midostaurin is not funded in most provinces in Canada, and compassionate programs are extremely limited. Given that the annual out of pocket cost often exceeds $100 000 CAD, midostaurin is not a realistic treatment option for most patients in Canada.

Avapritinib is a potent and selective inhibitor of the *KIT* D816V mutation that has been studied in the phase I EXPLORER and phase II PATHFINDER trials in adult patients with advanced SM.[34,37] The interim analysis of the PATHFINDER trial showed an ORR of 75% at a median follow-up of 10.4 months and the estimated 12-month PFS and OS rates were 79% and 86%, respectively, at a median follow-up of 7 months. Intracranial bleeding was observed in 13% of patients in the EXPLORER trial and was strongly associated with severe thrombocytopenia[34]; as a result, both studies were amended to exclude patients with severe thrombocytopenia, and avapritinib is recommended for patients with a platelet count of 50,000/mm^3 or higher. Avapritinib was approved in the US in 2021 and in Europe in 2022 for the treatment of advanced SM but is not currently available in Canada.

Cladribine, while not approved by Health Canada for SM, is used off label for all variants of advanced SM. Studies have shown that cladribine has an ORR of approximately 50–77% for patients with advanced SM with a median duration of response of approximately 1–2.5 years. Infectious complications and myelosuppression are the main adverse events.[38–40]

Peginterferon alfa-2a is also used off label in Canada for patients with ASM and SM-AHN (when the SM component requires treatment); however, it is not recommended for MCL.[28] It may also be useful in some patients with ISM or SSM who have severe or refractory mediator or bone symptoms.[28]

Imatinib is approved by Health Canada for advanced SM for those without the *KIT* D816V mutation or whose *KIT* mutational status is unknown; however, since >90% of patients with SM have the *KIT* D816V mutation, imatinib has a limited role in the treatment of SM.[41]

There is a paucity of high-quality data on the role of allogenic hematopoietic stem cell transplant for patients with SM. Typically, this treatment is reserved for patients with aggressive/refractory disease and for those with SM-AHN with high-risk AHN features (e.g. AML). The role of KIT inhibitors in the post-transplant setting has not been formally studied in prospective trials.[37,42]

Prognosis

Accurate staging of SM as described above is important for prognostication, but it is worth noting that most of the long-term survival data is from the pre-TKI treatment era.[27] Non advanced forms of SM are comparatively slow growing neoplasms and patients tend to have excellent long-term survival, ranging from a median OS not reached for BMM, 25–28 years for ISM, and 12 years for SMM.[38,43,44] In ISM, the estimated rate of transformation to advanced SM and leukemic transformation is <3% and <1%, respectively.[38,43,44] In advanced forms of SM, the median OS varies, with a range from approximately 3–6 years for those with ASM, 2–3 years for those with SM-AHN, and 2 months–2 years for those with MCL.[28,38,45,46] Leukemic transformation in ASM and SM-AHN is variable, and is impacted greatly by the AHN component, with an overall risk ranging from 6–30%.[38] Prognostic models have been developed that integrate clinical and molecular variables, although the performance of these models in the TKI era is not well defined.[27,28]

Conclusion

SM is a rare malignancy with a wide spectrum of clinical presentations and natural histories. The pathogenesis of SM is strongly linked to somatic KIT-activating mutations leading to **(1)** excessive MC activation, and **(2)** MC accumulation in tissues, which can lead to organ dysfunction and a high symptom burden that greatly impacts morbidity and/or mortality. Management requires multidisciplinary care, and while treatment options are expanding, they remain very limited in Canada, which is an enormous unmet need.

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Financial Disclosures:

Consultancy and Advisory Board:
Medison Pharma

References

1. van Doormaal JJ, Arends S, Brunekreeft KL, van der Wal VB, Sietsma J, van Voorst Vader PC, et al. Prevalence of indolent systemic mastocytosis in a Dutch region. J Allergy Clin Immunol. 2013;131(5):1429-1431.e1421. doi:10.1016/j.jaci.2012.10.015
2. Cohen SS, Skovbo S, Vestergaard H, Kristensen T, Møller M, Bindslev-Jensen C, et al. Epidemiology of systemic mastocytosis in Denmark. Br J Haematol. 2014;166(4):521-528. doi:10.1111/bjh.12916
3. Lim KH, Tefferi A, Lasho TL, Finke C, Patnaik M, Butterfield JH, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood. 2009;113(23):5727-5736. doi:10.1182/blood-2009-02-205237
4. Kirshenbaum AS, Kessler SW, Goff JP, Metcalfe DD. Demonstration of the origin of human mast cells from CD34+ bone marrow progenitor cells. J Immunol. 1991;146(5):1410-1415.
5. Galli SJ, Kalesnikoff J, Grimbaldeston MA, Piliponsky AM, Williams CM, Tsai M. Mast cells as "tunable" effector and immunoregulatory cells: recent advances. Annu Rev Immunol. 2005;23:749-786. doi:10.1146/annurev.immunol.21.120601.141025
6. Galli SJ, Tsai M. Mast cells: versatile regulators of inflammation, tissue remodeling, host defense and homeostasis. J Dermatol Sci. 2008;49(1):7-19. doi:10.1016/j.jdermsci.2007.09.009
7. Metcalfe DD, Baram D, Mekori YA. Mast cells. Physiol Rev. 1997;77(4):1033-1079. doi:10.1152/physrev.1997.77.4.1033
8. Miettinen M, Lasota J. KIT (CD117): a review on expression in normal and neoplastic tissues, and mutations and their clinicopathologic correlation. Appl Immunohistochem Mol Morphol. 2005;13(3):205-220. doi:10.1097/01.pai.0000173054.83414.22
9. Furitsu T, Tsujimura T, Tono T, Ikeda H, Kitayama H, Koshimizu U, et al. Identification of mutations in the coding sequence of the proto-oncogene c-kit in a human mast cell leukemia cell line causing ligand-independent activation of c-kit product. J Clin Invest. 1993;92(4):1736-1744. doi:10.1172/jci116761
10. Kitayama H, Kanakura Y, Furitsu T, Tsujimura T, Oritani K, Ikeda H, et al. Constitutively activating mutations of c-kit receptor tyrosine kinase confer factor-independent growth and tumorigenicity of factor-dependent hematopoietic cell lines. Blood. 1995;85(3):790-798.
11. Metcalfe DD. Mast cells and mastocytosis. Blood. 2008;112(4):946-956. doi:10.1182/blood-2007-11-078097
12. González de Olano D, de la Hoz Caballer B, Núñez López R, Sánchez Muñoz L, Cuevas Agustín M, Diéguez MC, et al. Prevalence of allergy and anaphylactic symptoms in 210 adult and pediatric patients with mastocytosis in Spain: a study of the Spanish network on mastocytosis (REMA). Clin Exp Allergy. 2007;37(10):1547-1555. doi:10.1111/j.1365-2222.2007.02804.x
13. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. Allergy. 2008;63(2):226-232. doi:10.1111/j.1398-9995.2007.01569.x
14. Alvarez-Twose I, Zanotti R, González-de-Olano D, Bonadonna P, Vega A, Matito A, et al. Nonaggressive systemic mastocytosis (SM) without skin lesions associated with insect-induced anaphylaxis shows unique features versus other indolent SM. J Allergy Clin Immunol. 2014;133(2):520-528. doi:10.1016/j.jaci.2013.06.020
15. Niedoszytko M, Bonadonna P, Oude Elberink JN, Golden DB. Epidemiology, diagnosis, and treatment of Hymenoptera venom allergy in mastocytosis patients. Immunol Allergy Clin North Am. 2014;34(2):365-381. doi:10.1016/j.iac.2014.02.004
16. Jimenez-Rodriguez TW, Garcia-Neuer M, Alenazy LA, Castells M. Anaphylaxis in the 21st century: phenotypes, endotypes, and biomarkers. J Asthma Allergy. 2018;11:121-142. doi:10.2147/jaa.S159411
17. Valent P. Risk factors and management of severe life-threatening anaphylaxis in patients with clonal mast cell disorders. Clin Exp Allergy. 2014;44(7):914-920. doi:10.1111/cea.12318
18. van Anrooij B, van der Veer E, de Monchy JG, van der Heide S, Kluin-Nelemans JC, van Voorst Vader PC, et al. Higher mast cell load decreases the risk of Hymenoptera venom-induced anaphylaxis in patients with mastocytosis. J Allergy Clin Immunol. 2013;132(1):125-130. doi:10.1016/j.jaci.2012.12.1578
19. Gulen T, Hägglund H, Dahlén B, Nilsson G. Mastocytosis: The puzzling clinical spectrum and challenging diagnostic aspects of an enigmatic disease. Journal of Internal Medicine. 2015;279. doi:10.1111/joim.12410
20. van der Veer E, van der Goot W, de Monchy JG, Kluin-Nelemans HC, van Doormaal JJ. High prevalence of fractures and osteoporosis in patients with indolent systemic mastocytosis. Allergy. 2012;67(3):431-438. doi:10.1111/j.1398-9995.2011.02780.x
21. Degboé Y, Eischen M, Nigon D, Apoil PA, Mailhol C, Tournier E, et al. Prevalence and risk factors for fragility fracture in systemic mastocytosis. Bone. 2017;105:219-225. doi:10.1016/j.bone.2017.09.005
22. Riffel P, Schwaab J, Lutz C, Naumann N, Metzgeroth G, Fabarius A, et al. An increased bone mineral density is an adverse prognostic factor in patients with systemic mastocytosis. J Cancer Res Clin Oncol. 2020;146(4):945-951. doi:10.1007/s00432-019-03119-3

23. Acosta-Mérida Á, Ojeda-Bruno S. Multiple vertebral fractures as the first manifestation of systemic mastocytosis. Osteoporos Int. 2019;30(5):1121-1124. doi:10.1007/s00198-019-04897-9
24. Hartmann K, Escribano L, Grattan C, Brockow K, Carter MC, Alvarez-Twose I, et al. Cutaneous manifestations in patients with mastocytosis: Consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology. J Allergy Clin Immunol. 2016;137(1):35-45. doi:10.1016/j.jaci.2015.08.034
25. Berezowska S, Flaig MJ, Ruëff F, Walz C, Haferlach T, Krokowski M, et al. Adult-onset mastocytosis in the skin is highly suggestive of systemic mastocytosis. Mod Pathol. 2014;27(1):19-29. doi:10.1038/modpathol.2013.117
26. Veitch S, Radia DH. Mastocytosis demystified. Hematology Am Soc Hematol Educ Program. 2023;2023(1):396-406. doi:10.1182/hematology.2023000505
27. Pardanani A. Systemic mastocytosis in adults: 2023 update on diagnosis, risk stratification and management. Am J Hematol. 2023;98(7):1097-1116. doi:10.1002/ajh.26962
28. National Comprehensive Cancer Network. Systemic Mastocytosis. [accessed 2024 February 15, 2024]. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1490.
29. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, 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. doi:10.1038/s41375-022-01613-1
30. Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka HM, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228. doi:10.1182/blood.2022015850
31. Swerdlow SH, Campo E, Harris NL, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition. IARC, Lyon, 2017
32. González de Olano D, Alvarez-Twose I, Esteban-López MI, Sánchez-Muñoz L, de Durana MD, Vega A, et al. Safety and effectiveness of immunotherapy in patients with indolent systemic mastocytosis presenting with Hymenoptera venom anaphylaxis. J Allergy Clin Immunol. 2008;121(2):519-526. doi:10.1016/j.jaci.2007.11.010
33. Bonadonna P, Gonzalez-de-Olano D, Zanotti R, Riccio A, De Ferrari L, Lombardo C, et al. Venom immunotherapy in patients with clonal mast cell disorders: efficacy, safety, and practical considerations. J Allergy Clin Immunol Pract. 2013;1(5):474-478. doi:10.1016/j.jaip.2013.06.014
34. DeAngelo DJ, George TI, Linder A, Langford C, Perkins C, Ma J, et al. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. Leukemia. 2018;32(2):470-478. doi:10.1038/leu.2017.234
35. Gotlib J, Kluin-Nelemans HC, George TI, Akin C, Sotlar K, Hermine O, et al. Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis. N Engl J Med. 2016;374(26):2530-2541. doi:10.1056/NEJMoa1513098
36. DeAngelo DJ, Radia DH, George TI, Robinson WA, Quiery AT, Drummond MW, et al. Safety and efficacy of avapritinib in advanced systemic mastocytosis: the phase 1 EXPLORER trial. Nat Med. 2021;27(12):2183-2191. doi:10.1038/s41591-021-01538-9
37. Gotlib J, Reiter A, Radia DH, Deininger MW, George TI, Panse J, et al. Efficacy and safety of avapritinib in advanced systemic mastocytosis: interim analysis of the phase 2 PATHFINDER trial. Nat Med. 2021;27(12):2192-2199. doi:10.1038/s41591-021-01539-8
38. Lim KH, Pardanani A, Butterfield JH, Li CY, Tefferi A. Cytoreductive therapy in 108 adults with systemic mastocytosis: Outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine. Am J Hematol. 2009;84(12):790-794. doi:10.1002/ajh.21561
39. Tefferi A, Kittur J, Farrukh F, Begna KH, Patnaik MM, Al-Kali A, et al. Cladribine therapy for advanced and indolent systemic mastocytosis: Mayo Clinic experience in 42 consecutive cases. Br J Haematol. 2022;196(4):975-983. doi:10.1111/bjh.17932
40. Barete S, Lortholary O, Damaj G, Hirsch I, Chandesris MO, Elie C, et al. Long-term efficacy and safety of cladribine (2-CdA) in adult patients with mastocytosis. Blood. 2015;126(8):1009-1016; quiz 1050. doi:10.1182/blood-2014-12-614743
41. Shomali W, Gotlib J. Response criteria in advanced systemic mastocytosis: evolution in the era of KIT inhibitors. Int J Mol Sci. 2021;22(6). doi:10.3390/ijms22062983
42. Ustun C, Gotlib J, Popat U, Artz A, Litzow M, Reiter A, et al. Consensus opinion on allogeneic hematopoietic cell transplantation in advanced systemic mastocytosis. Biol Blood Marrow Transplant. 2016;22(8):1348-1356. doi:10.1016/j.bbmt.2016.04.018
43. Escribano L, Alvarez-Twose I, Sánchez-Muñoz L, Garcia-Montero A, Núñez R, Almeida J, et al. Prognosis in adult indolent systemic mastocytosis: a long-term study of the Spanish Network on Mastocytosis in a series of 145 patients. J Allergy Clin Immunol. 2009;124(3):514-521. doi:10.1016/j.jaci.2009.05.003
44. Trizuljak J, Sperr WR, Nekvindová L, Elberink HO, Gleixner KV, Gorska A, et al. Clinical features and survival of patients with indolent systemic mastocytosis defined by the updated WHO classification. Allergy. 2020;75(8):1927-1938. doi:10.1111/all.14248
45. Pardanani A, Lim KH, Lasho TL, Finke CM, McClure RF, Li CY, et al. WHO subvariants of indolent mastocytosis: clinical details and prognostic evaluation in 159 consecutive adults. Blood. 2010;115(1):150-151. doi:10.1182/blood-2009-10-249979
46. Sperr WR, Kundi M, Alvarez-Twose I, van Anrooij B, Oude Elberink JNG, Gorska A, et al. International prognostic scoring system for mastocytosis (IPSM): a retrospective cohort study. Lancet Haematol. 2019;6(12):e638-e649. doi:10.1016/S2352-3026(19)30166-8