Diagnosis and Treatment of Systemic Mastocytosis in Brazil:
Recommendations of a Multidisciplinary Expert Panel

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INTRODUCTION

Mastocytosis is a group of neoplastic disorders characterized by expanding and accumulating clonal and neoplastic mast cells (MCs) in the skin and/or various internal organs, such as the bone marrow, spleen, lymph nodes, and gastrointestinal tract[1]. The updated 2016 World Health Organization broadly classifies mastocytosis into cutaneous and systemic forms. In cutaneous mastocytosis (CM), MCs are restricted to the skin, whereas systemic mastocytosis (SM) refers to systemic involvement of several organs by neoplastic MCs. SM is more common in adults than children and is a highly heterogeneous disease, both in clinical presentation and prognosis. Life expectancy for patients with SM can range from normal or near-normal to severely reduced, depending on the aggressiveness of the disease[2].
Although published international consensuses of experts on the diagnosis and management of patients with SM exist, there have been no guidelines published on managing this disease in Brazil, a low and middle-income (LMIC) country. This study aims to establish an expert panel's recommendations regarding the diagnosis and management of SM adapted to the reality of the country.

METHODS

Eighteen Brazilian experts (including haematologists, immunologists, and dermatologists) met online on May 15th, 2021, to discuss relevant clinical questions regarding the diagnosis, treatment, and follow-up of patients with SM. Thirty multiple choice questions, previously defined by 5 of these specialists (area coordinators), were submitted for discussion and voting. A recommendation was established if at least 75% of the panel agreed with an answer. If less than 75% but greater than 49% agreement was achieved, a suggestion was presented. No recommendations or suggestions were made if there was less than 50% agreement. The Oxford 2011 Levels of Evidence[3] document was used to grade the expert panel's recommendations and suggestions.

RESULTS AND DISCUSSION

DIAGNOSIS AND CLASSIFICATION

Mastocytosis is a clonal proliferation of abnormal MCs that accumulate in one or more organs[4]. The clinical presentation of mastocytosis is heterogeneous, ranging from skin- limited disease (CM) to a more aggressive variant with extra-cutaneous involvement (SM). Criteria for diagnosis were developed by the WHO in 2001, with the last update in 2016[5]. Table 1 shows the current WHO criteria for SM diagnosis and Table 2 the current mastocytosis classification. Figure 1 illustrates several clinical and laboratory features of this disease.
A small study of 24 patients[6] found that although all WHO criteria have high specificity (100%), the sensitivity of individual criteria varied from 69% for bone marrow biopsy histopathologic findings to 92% for the presence of an aberrant phenotype in bone marrow aspirate. These findings led to low negative predictive values in the studied population, ranging from 38% to 75% for the same criteria mentioned above.
The sensitivity of *KIT* mutation testing for SM diagnosis may be enhanced by enriching the sample for abnormal MCs by using laser capture microdissection[7], magnetic bead-156 based, FACS-based cell sorting, and other techniques with higher sensitivity[8].
Suggestion: New or modified diagnostic criteria with higher sensitivity should be included in future revisions of the WHO criteria to diagnose Systemic Mastocytosis (GRADE 3).

It is estimated that most adult patients with mastocytosis have SM[9] but that isolated cutaneous disease is more prevalent in paediatric patients[10]. Skin manifestations are observed in approximately 80% of adult patients with SM[11], but a specific population may present with a subvariant form of indolent SM (ISM) with bone marrow involvement only[4]. SM should always be suspected and investigated in adult patients with cutaneous disease[12].
Bone marrow biopsy is rarely performed for children[9], but a recent review suggests that systemic involvement should be investigated in selected cases[13].
Cutaneous Mastocytosis (CM) is defined by typical skin lesions of mastocytosis associated with Darier's sign (major criterion) and one or two of the following criteria[14, 15]:
1. Increased numbers of mast cells in biopsy sections of lesional skin (approximately 40 mast cells/mm2);
2. (Activating) *KIT* mutation in skin lesion. However, it should be noted that at present, only a few laboratories are able to sequence *KIT* from skin tissue biopsy.

CM is classified based on macroscopic features and the pattern of distribution of skin lesions. In contrast to Maculopapular Cutaneous Mastocytosis (MPCM) and diffuse CM, mastocytomas are almost never observed in adults[14].
Patients with SM often also present with cutaneous involvement, which is characterized by erythematous-brown fixed maculopapular cutaneous lesions. Adults with ISM usually manifest monomorphic maculopapular lesions, whereas children with CM develop polymorphic maculopapular lesions.
Maculopapular skin lesions found in patients with ISM and those with CM also occur in patients with advanced SM. It is estimated that approximately 80% of patients with ISM exhibit maculopapular skin lesions compared with only approximately 50% of patients with advanced SM[16].
Recommendation: Cutaneous Mastocytosis should be diagnosed only after dermatological clinical evaluation, anatomopathological examination, and detection of Systemic Mastocytosis criteria (GRADE 1).
Tryptase is a serine protease predominantly produced by tissue mast cells and is the most specific marker of MC activation and burden[16]. Elevated serum tryptase can be found in several clinical conditions and diseases[16, 17].
In SM, a persistently elevated serum tryptase level (>20 ng/ml) is a minor diagnostic criterion in the WHO diagnostic framework; levels vary widely, but serum tryptase is elevated in the vast majority of SM patients across all WHO subgroups. A significantly greater proportion of Aggressive Systemic Mastocytosis (ASM) and Systemic Mastocytosis with an Associated Clonal Haematological Non-Mast Cell Lineage Neoplasm (SM-ANHN) patients exhibit a markedly elevated serum tryptase level (>200 ng/ml) than those with ISM[18]. Patients with CM, except for cases with extensive skin involvement, typically exhibit normal levels of total tryptase, and serum tryptase has been shown to be a sensitive marker for SM diagnosis[16, 19, 20].
Serum basal levels of tryptase also correlate with disease progression and response to treatment[21] and therefore should be tested periodically, particularly in advanced cases.

Recommendation: Tryptase level measurements are necessary for Systemic Mastocytosis diagnosis and follow-up (GRADE 2) at least once a year (GRADE 5).
In patients with SM, the bone marrow is the organ most targeted by MCs. Evaluation of bone marrow, including bone marrow aspirate, immunophenotyping by flow cytometry, and histopathological evaluation of bone marrow biopsy, can detect infiltration by neoplastic, abnormal MCs and is one of the cornerstones for diagnosis of SM by the WHO SM criteria[4, 5]. Indeed, according to the 2016 WHO Classification, detection of multifocal dense infiltrates of MCs (≥15 mast cells in aggregates) in the bone marrow is a major criterion for SM diagnosis. The presence of atypical morphology in more than 25% of MCs, including spindle-shaped MCs, is considered a minor criterion[5]. Thus, bone marrow evaluation by unilateral bone marrow biopsy with a histopathological review, preferably by a pathologist with expertise in recognizing MC disorders, is mandatory[4, 5, 22].
Moreover, immunophenotyping evaluation of MCs can help detect small infiltrates that are not readily apparent in the morphological evaluation of the marrow biopsy[21,23]. Immunohistochemical staining for CD117 and tryptase can readily detect the presence of small MC aggregates but cannot distinguish between normal and neoplastic MCs25. Expression of CD25 and/or CD2 can help in the differentiation of normal (negative for these markers) and neoplastic (positive for these markers) MCs25, and expression of CD25 and CD2 is also considered a minor criterion by the 2016 WHO Classification[5]. Of the two markers, CD25 appears to be the most reliable, being found in most cases of both advanced and indolent SM[24]. CD25 and CD2 can be evaluated by immunohistochemistry in the marrow biopsy and/or by flow cytometry.
Most patients with systemic mastocytosis harbour mutations in the *KIT* gene, which encodes the stem cell factor receptor CD117, a class III receptor tyrosine kinase expressed by MCs, haematopoietic progenitor cells, germ cells, melanocytes, and interstitial cells of Cajal in the gastrointestinal tract[27]. The gain-of-function D816V mutation in the *KIT* gene is detected in most (>95%) adult patients with SM[28]. Other *KIT* mutations are found in paediatric patients with CM[29] and a minority of adult SM patients[4]. Some of these other *KIT* mutations and the rare case of SM with wild-type *KIT* may involve disease that is responsive to the tyrosine kinase inhibitor imatinib[28, 30].
The D816V *KIT* mutation allele burden was also found to correlate with disease activity, disease subtype, and survival[28,32,33]. This mutation confers the receptor with a conformational modification, rendering cells resistant to imatinib[34]. Some patients with increased MCs and eosinophilia may carry the *FIP1L1-PDGFRA* fusion gene associated with imatinib sensitivity and should be mentioned that according to the 2016 WHO Classification, such disease would be classified as Myeloid/Lymphoid Neoplasm with *PDGFRA* rearrangement and not SM[5].
Analysis of *KIT* mutations in bone marrow cells is a standard diagnostic procedure for SM. In most patients with ISM, particularly those with ISM, the burden of neoplastic MCs in the bone marrow can be very low, so this may represent a technical challenge for detecting the mutation if only conventional detection methods are employed (e.g., Sanger sequencing)[35]. The sensitivity of *KIT* mutation testing for SM diagnosis may be enhanced by enriching the sample for neoplastic MCs by laser capture microdissection, magnetic bead-based, FACS-based cell sorting, or using digital allele-specific PCR techniques with high sensitivity[8,21].
Recommendation: D816V *KIT* mutations should be investigated in all patients with Systemic Mastocytosis. The *FIP1L1-PDGFRA* fusion gene needs to be investigated in patients with increased BM mast cells and eosinophilia (GRADE 2).

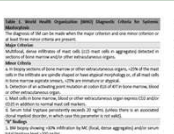
Imaging studies can determine the degree of mast cell infiltration in specific organs. Magnetic resonance imaging (MRI) is more sensitive than conventional X-rays in detecting bone marrow involvement, and a whole MRI body exam may also contribute to determining the presence of B/C-findings factors such as the presence of hepatosplenomegaly and ascites[36].
The most common bone abnormality in patients with SM is diffuse demineralization, which can be revealed by bone mineral density (BMD) of the lumbar spine and femur with the dual-energy X-ray absorptiometry (DEXA) technique[36]. Tc99 bone scintigraphy can detect diffuse bone involvement and a greater number of focal lesions, with a higher sensitivity than plain radiography[36].
Infiltration of the intestinal tract by MCs can be confirmed by biopsy during colonoscopy, but bowel involvement rarely correlates with symptoms[40]. Abdominal ultrasonography is the most common initial study in patients with SM to assess abdominal involvement[39]. Computed tomography (CT) scans are also used to detect abdominal signs of MC infiltration in the liver, spleen, and other abdominal organs[36,41]. Although the findings in patients with SM are not specific, they may be used to direct further studies for diagnostic confirmation and for estimating the extent of systemic involvement[42].
Positron emission tomography/computed tomography with 2-[fluorine-18]-fluoro-2- deoxy-D-glucose (FDG-PET/CT scan) has been shown in a multicentre study[43] and in a case series of five SM patients[44] to have little value in diagnosing or staging most forms of the disease. Higher uptake was detected in patients with SM-AHN, mast cell sarcoma (MCS)[43], and in a single case report of an MCL patient with extramedullary involvement[44].
Recommendation: Doppler abdominal ultrasound should be performed for all patients with Systemic Mastocytosis. The whole-body MRI scan should not be part of the initial assessment of the most common forms of the disease (GRADE 3).
Recommendation: CT scans and MRI should be used to evaluate Systemic Mastocytosis "C_" findings. FDG-PET/CT scans should not be part of the initial assessment of the most common forms of the disease (GRADE 3).

PROGNOSIS
The 2016 WHO classification of Systemic Mastocytosis is the most practical first step in determining prognosis for each case[4]. A study with 342 patients performed at the Mayo Clinic[45] validated the prognostic relevance of the WHO classification system; multivariable analysis showed a significant and independent association of inferior survival with WHO subtype (P <0.001), advanced age (P<0.001), weight loss (P<0.01), anaemia (P=0.007), thrombocytopaenia (P<.001), hypoalbuminaemia (P<.001), and 297 excess BM blasts (>5%; P=0.004). In a more recent analysis of patients, the Mayo Alliance Prognostic System(MAPS) developed a hybrid clinicomolecular model that included age >60 years, WHO-defined advanced SM, thrombocytopenia <150x109/L, increased serum ALP, and anemia (defined as a haemoglobin level below the sex- adjusted normal reference range) or adverse mutations (*ASXL1*, *RUNX1*, *NRAS*). Survival correlated directly and proportionally with the number of risk factors[27].
Recommendation: The clinical or hybrid Mayo criteria should be used to determine prognosis (GRADE 4).

TREATMENT AND FOLLOW-UP
Treatment of SM should be individualized and varies from a watch and wait period to symptom management, supportive measures, and cytoreductive therapy for MC debulking in the setting of aggressive, advanced, or treatment-refractory disease[4]. Allogeneic stem cell transplantation is another option for patients with SM-AHN or ASM[46,47].
Symptomatic treatment aims to manage symptoms efficiently and minimize their recurrence. Avoidance of triggers and use of prophylactic medication when risk avoidance is difficult or impossible are necessary first measures for symptomatic control[48]. Mastocytosis symptoms can be divided into skin symptoms, mast cell mediator "release" symptoms, and symptoms caused by MC infiltration in various organs[49].
Treatment of mild clinical manifestations is mainly symptomatic and consists of the following: H1-histamine receptor blockers for general symptoms; H2-histamine receptor blockers, mainly for gastrointestinal symptoms; leukotriene receptor blockers and mast cell stabilizers49. Glucocorticoids may be useful in treating SM for acute reactions, though long-term adverse effects may limit their use. Cutaneous manifestations may also respond to topical corticosteroids and calcineurin inhibitors51. See Table 3 for treatment of cutaneous symptoms in SM.
Brazzelli *et al.* published a research report on 20 patients with CM and ISM treated with PUVA therapy (UVA plus psoralen therapy) and NB-UVB (narrowband UVB), with good results. In general, however, this is a method of limited efficacy, and only partial and temporary improvement of skin signs and symptoms can be achieved. The carcinogenic effect of phototherapy and photochemotherapy should also be considered, particularly with long-term or recurrent ultraviolet phototherapy, which is needed to achieve a skin response in CM.
Melanoma incidence seems to be elevated in patients with mastocytosis52, and careful monitoring of premalignant skin lesions should be carried out periodically53.

Recommendation: Treatment of cutaneous disease should focus on symptomatic relief and trigger avoidance (GRADE 2).
Recommendation: Antihistamines should be used for symptomatic treatment (GRADE 2).
Suggestion: Antihistamines may be used for prophylactic treatment, especially in highly symptomatic patients (GRADE 2).
Recommendation: Follow-up in patients with indolent or smouldering Systemic Mastocytosis should include symptomatic management and bone disease measurement (GRADE 3).

Recommendation: Dermatological examination should be performed at least once a year. Emollients, insect repellents, H1 ± H2 antihistamines, sunscreens, ketotifen, and cromoglycate* are the basis of treatment (GRADE 4) *(GRADE 2)



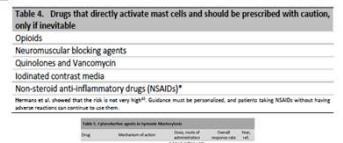
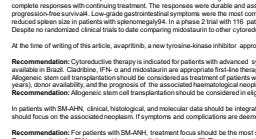
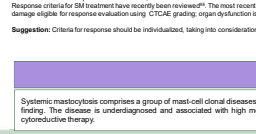
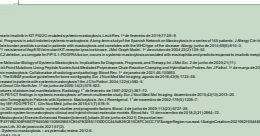


Table 4. Drugs that directly activate mast cells and should be prescribed with caution, only if inevitable

- Opioids
- Neuromuscular blocking agents
- Quinolones and Vancomycin
- Iodinated contrast media
- Non-steroid anti-inflammatory drugs (NSAIDs)*

Bernars et al. showed that the risk is not very high[54]. Guidance must be personalized, and patients taking NSAIDs without having adverse reactions can continue to use them.