


REVIEW

Mastocytosis: One Word for Different Diseases

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ABSTRACT

Mastocytosis is a neoplastic disease originating from tissue infiltration by transformed mast cells. The diagnosis requires a high grade of suspicion due to the large variety of presenting symptoms. The World Health Organization classification recognizes localized (cutaneous) and systemic forms of the disease, with these forms showing different degrees of aggressiveness. Mastocytosis is often a multiorgan disease, and its correct management requires a multidisciplinary team of experienced consultants to provide overall patient care. Bone marrow evaluation by molecular analyses, skeleton X-ray and abdominal scan together with allergologic and dermatologic evaluation constitute the essential diagnostic work-up for adult patients with mastocytosis. As clinical

situations vary, treatment options range from the use of drugs to treat the symptoms, such as anti-H1 receptors and steroids, to UV irradiation, which is overwhelmingly used in patients with cutaneous mastocytosis (CM) or indolent systemic mastocytosis, to cytoreductive treatment to control life-threatening symptoms or organ damage in the more aggressive forms of the disease. Prognosis also widely differs among patients diagnosed with mastocytosis, with the spectrum ranging from an almost normal life expectancy for those with CM and to less than 1-year median overall survival for those with mast cell leukemia.

Keywords: Anaphylaxis; Cladribine; Invasive procedures; Mastocytosis; Pregnancy; Systemic mastocytosis

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INTRODUCTION

The term mastocytosis refers to a wide range of neoplastic diseases originating from the infiltration of tissue by transformed mast cells. The signs, symptoms and clinical presentations, which are highly variable, depend on the distinct functions of the mast cells that are involved in the acute phase of inflammation and mediate allergic response.

Mast cells are normally present in the skin, gastro-intestinal (GI) tract and bone marrow,

where their contact with endogenous or exogenous antigens leads to the release of several mediators acting on endothelial, smooth muscle and nervous cells and subsequent recruitment of other inflammation cells. Abnormal activity of mast cells causes hypersensitivity diseases, such as augmented allergic reactions, asthma and urticaria, but also plays a role in autoimmune diseases and chronic skin inflammation. When a neoplastic transformation occurs, mast cells accumulate prevalently in the skin and bone marrow and are responsible for the allergic symptoms that are in most cases the main complaints of patients.

The incidence of mastocytosis is not known due to rarity of disease and protean clinical manifestations, but it has been reported in a Danish study to be 0.89 per 100,000/year [1].

The diagnosis of mastocytosis requires a high grade of suspicion because the presenting symptoms may vary from the most reported symptoms, such as facial flushing and dizziness, skin reddish lesions and pruritus, respiratory discomfort with breath difficulties, to constitutional (sweating, fatigue, palpitation), GI (nausea, vomiting, abdominal pain, diarrhea), musculoskeletal and neurological symptoms (myalgia, bone pain and fractures, headache, depression and panic attack) and to hypotension, syncope and life-threatening anaphylactic shock. Attacks of mast cell degranulation are often unpredictable and can be triggered by physical factors, such as heat/cold variation and physical exertion, the consumption of certain food and/or alcohol, the use of drugs, such as nonsteroidal anti-inflammatory drugs, emotional stress and hymenoptera venoms.

The aim of this paper was to review the World Health Organization (WHO) classification, clinical characteristics and management of adult mastocytosis. This review is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

WHO CLASSIFICATION

In the most recent WHO classification of mastocytosis, the disorder was included in the

group of myeloproliferative neoplasms [2] (Table 1). However, several nosological entities are recognized, and expert panels frequently revise the classification [3].

Cutaneous mastocytosis (CM) is defined as an isolated skin infiltration without signs of bone marrow involvement that typically presents with small, round, reddish or brown lesions. CM most frequently presents as maculopapular CM (also known as urticaria pigmentosa), with two variants, namely, monomorphic and polymorphic infiltrates. More rare presentations are diffuse CM and cutaneous mastocytoma [3]. The flare-up of lesions but not of normal skin after moderate rubbing, referred to as Darier's sign, is evocative of disease and is a reliable physical finding. Minor criteria of CM are an increased number of mast cells and the identification of mutations causing constitutive activation of the oncogenic tyrosine kinase KIT in abnormal tissue, even if the number of mast cells in healthy skin varies according to cutis layers and parts of the body [4]. CM is typically found in children and tends to disappear during adolescence; isolated CM is only rarely found in adults, and when found it is often associated to bone marrow involvement.

Systemic mastocytosis (SM) is characterized by the presence of multifocal dense infiltrates, each composed of at least 15 mast cells, identified in the bone marrow and/or other extracutaneous organs (Table 2). Minor essential criteria are an atypical or immature morphology, presence of mutations causing constitutive activation of KIT based on molecular analysis, abnormal CD2 and/or CD25 expression based on flow cytometry analysis and constant serum tryptase level at > 20 ng/ml. A diagnosis of SM can be made if the major criterion and one of more of the minor criteria are met. According to markers of high burden disease (B findings: $> 30\%$ infiltration in the bone marrow, a serum tryptase level of > 200 ng/ml, signs of dysplasia or proliferation not diagnostic of another hematological malignancy [HM], abnormal size of the liver, spleen or lymph nodes without impaired function) or of end organ damage (C findings: cytopenia due to massive bone marrow infiltration, impaired liver function with ascites and/or portal hypertension,

Table 1 World Health Organization of mastocytosis

WHO categories	Subtypes	Diagnostic criteria	Characteristics
Cutaneous mastocytosis	Urticaria pigmentosa	Immunohistochemistry	Reddish papular lesions
	Diffuse cutaneous mastocytosis		Reddish diffuse thickening of skin
	Solitary mastocytoma of skin		Brownish-yellow, minimally elevated plaque
Systemic mastocytosis	Indolent SM	Diagnostic criteria of SM	No C findings ^a At least 2 B findings ^a and no C findings Isolated BM mastocytosis
	Aggressive SM		At least one C findings
	SM associated to associated clonal hematological non mast cell lineage disease		WHO criteria for a clonal hematological neoplasm
Mast cell leukemia		Diagnostic criteria of SM	BM smear > 20% MC BM biopsy diffuse infiltration of immature MC PB smear > 10% MC
Mast cell sarcoma		No criteria for SM	Isolated MC tumor Destructive growth pattern
Extracutaneous mastocytoma		No criteria for SM	Isolated MC tumor Non-destructive growth pattern

BM Bone marrow, MC mast cells, PB peripheral blood, SM systemic mastocytosis, WHO World Health Organization

^a See text and Table 2 for description of B and C findings

hypersplenism, osteolytic bone lesions and/or pathological fractures, malabsorption and weight loss), SM is further classified as indolent SM (ISM; no B or C findings), smoldering SM (SSM, at least two B findings but no C findings) and aggressive SM (ASM, at least one C finding).

Two other categories of SM are SM associated to a clonal hematological non-mast cell lineage disease (SM-AHNMD) in which WHO diagnostic criteria for another HM are satisfied, and mast cell leukemia (MCL), in which > 20% and

> 10% mast cells are recorded in bone marrow aspirate and peripheral blood smears, respectively.

In patients with symptoms of hypersensitivity and an abnormal MC population expressing CD2 and/or CD25 and/or mutations causing constitutive activation of KIT and < 15 mast cells in small aggregates, the correct diagnosis is monoclonal mast cell activation syndrome.

Table 2 World Health Organization diagnostic criteria for systemic mastocytosis

Diagnostic criteria	Organs	Characteristics
Major criteria	BM	Multifocal, dense infiltrate of > 15 aggregated MC
	Others (except skin)	
Minor criteria	BM	Immature and/or atypical MC > 25% in aggregates
	Others (except skin)	Spindle-shaped and/or atypical MC > 25% in aggregates
	BM, PB, others (except skin)	Activating mutation at codon 816
		Surface expression of CD2 and/or CD25 together with MC markers
B findings	Serum	Total tryptase persistently > 20 ng/ml
	BM	Infiltration > 30% MC Dysplasia or myeloproliferation insufficient for diagnosis of AHNMD Almost normal blood count
C findings	Liver, spleen, nodes	Enlargement without impaired function
	BM	Cytopenia without other hematological neoplasm
	Liver	Impaired function Ascites Portal hypertension
	Bones	Osteolysis Pathological fractures
	Spleen	Enlargement and hypersplenism
	GI	Malabsorption Weight loss

AHNMD Associated clonal hematological non-mast cell lineage disease, *GI* gastro-intestinal

CLINICAL PRESENTATION

Cutaneous Lesions

The most frequent presentation of adult mastocytosis is the appearance of small reddish or brown maculopapular lesions, starting from the lower trunk and thigh and generally spreading to all of the body surface except the face. Differently from childhood onset, where lesions are typically polymorphic, are not associated with organ infiltration and disappear after puberty in most cases, adult mastocytosis is almost always associated with bone marrow

involvement. On the other hand, cutaneous involvement may lack in advanced SM [3].

Patients presenting with evocative lesions should undergo skin biopsy to confirm neoplastic mast cell infiltration: this condition is referred to as mastocytosis in the skin (MIS) before involvement of other organs can be excluded by bone marrow evaluation with flow cytometry and molecular and immunohistochemistry analyses.

Anaphylaxis

Anaphylaxis is a potentially life-threatening hypersensitivity reaction involving at least two

of the following: cutaneous, cardiovascular and respiratory systems and GI tract. Although the prevalence of allergy in patients with mastocytosis is comparable to that in the general population [5, 6], the former show an increased prevalence of anaphylaxis; moreover, anaphylaxis can be the presenting symptom, especially in patients without MIS. Anaphylaxis can be triggered by a Hymenoptera sting, food, drugs, anxiety, hot or cold exposure, rapid change of room temperature and/or exercise [7, 8]. In a recent study in which 3374 patients complaining of an allergic disease were referred to outpatient clinic, tests for serum tryptase showed levels of > 15 ng/ml in 3% (96) of patients. Among these 96 patients, 30 showed persistently elevated serum tryptase levels of > 20 ng/ml, with 15 showing mast cell infiltration diagnostic for mastocytosis (12 cases of SM and 3 cases of CM). Moreover, the elevated level of tryptase in these patients was statistically significantly higher than that found in other hypersensitivity conditions [9].

In recent years, an association has been found between anaphylaxis, tryptase levels and mastocytosis. Bonadonna et al. recently evaluated 379 patients with a systemic reaction due to Hymenoptera venom and showed that 44 of these patients (11.6%) had a serum tryptase level that was persistently above the normal value (11.4 ng/ml) [10]. Taking into consideration that mastocytosis is a risk factor for anaphylaxis after Hymenoptera stings [10], they also performed bone marrow evaluation in 34 of 43 adult patients; according to cut-off value used, clonal mast cell disease was diagnosed in 50% and 88% of the evaluated patients with serum tryptase levels of > 20 ng/ml and > 11.4 ng/ml respectively [11].

In adult patients, neither the extent of cutaneous involvement or allele burden of the KIT D816 V mutation correlates with risk of anaphylaxis [8, 12], while levels of serum tryptase seem to be higher among patients with anaphylaxis [7].

Although performing a bone marrow biopsy may be resisted by these patients, there are sufficient evidence to validate the need for a complete diagnostic work-up in selected patients with anaphylaxis and a persistently

high serum tryptase, especially when specific immunoglobulin (Ig) E and allergy tests are negative. In the case of a diagnosis of SM it is important to start immunotherapy and to try to prevent situations and behavior that trigger attacks, as well as to schedule a timely follow-up considering the risk of disease progression.

Serum tryptase levels can be elevated at the onset of anaphylaxis and in the hours following onset. The correct time of evaluation is at least 2 days after complete resolution of the allergic symptoms. Moreover, allergic disorders, chronic infections by helminths and myeloid neoplasms should be considered in the differential diagnosis when evaluating a patient with persistently elevated serum tryptase level [13].

GI Symptoms

In some cases, patients may present with recurrent diarrhea and abdominal pain after meals that resemble symptoms of food intolerance or food allergy. In other cases, relapsing gastric ulcer or gastroesophageal reflux may suggest an underlying hypersecretion of mediators. Although these manifestations are not life-threatening, they can be debilitating and have a strong impact on the quality of life of patients [14]. Endoscopy and multiple biopsies should be performed, even in absence of evident mucosal alterations, to exclude infections, celiac disease or, more rarely, GI stromal tumors.

Bone Disease and Osteoporosis

Bone pain is a commonly reported symptom, and the link to mastocytosis can be extremely hard. However, osteoporosis of unclear origin should raise the suspicion of mastocytosis, especially among men. In a population-based study, the authors found an increased risk of osteoporosis as early as 3 years before the diagnosis of mastocytosis; this risk remained consistently higher than that in an age- and sex-matched non-SM population during a 10-year follow-up [15]. The risk of fractures was only slightly augmented compared to the control population [15]. First-line evaluation comprises

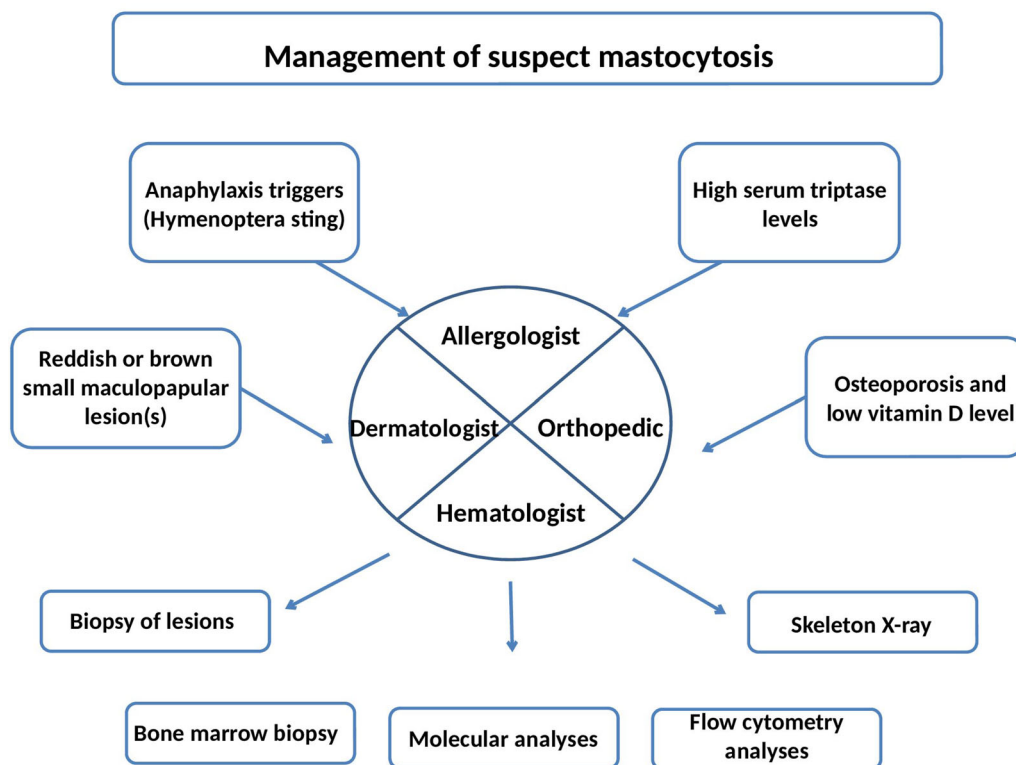


Fig. 1 Most frequent clinical presentations and required multidisciplinary approach for the management of suspected mastocytosis

dual-X-ray absorptiometry of the hip and lumbar vertebra for measuring bone mineral density and X-ray of the skeleton to exclude osteolysis and fractures.

In patients with persistent bone pain and unexplained osteoporosis, other clinical and/or laboratory findings to address the possible diagnosis of mastocytosis (skin lesions, serum tryptase) should be evaluated after the most relevant causes of osteoporosis are excluded. Therapy with oral bisphosphonates should be started according to their safety profile. In patients presenting with large osteolysis, a biopsy should be performed to exclude other neoplasms.

Leukemic Presentation

The first presentation of a mast cell disorder is only rarely a leukemic form. Symptoms are somewhat aspecific (weight loss, peripheral

edema, ascites) and/or evocative of acute bone marrow impairment and organ infiltration, and can worsen rapidly. Cytopenias and circulating mast cells are almost always detectable, and some systemic manifestation of hypersensitivity is not infrequent even if less frequently than in SM [16]. Prognosis is dismal, and chemotherapy should be performed.

MANAGEMENT

Mastocytosis is often a multiorgan disease, and its correct management requires a multidisciplinary team of experienced consultants to provide the overall care of patients (Fig. 1).

Molecular and Flow Cytometry Analyses

The detection of the KIT D816V mutation, a minor WHO diagnostic criterion, is mandatory when systemic mastocytosis is suspected. The

tyrosine kinase KIT is involved in hematopoiesis and is normally downregulated during lineage differentiation—the exception being in mast cells where its expression tends to remain high even in mature cells [17]. Activating mutations predominantly involve the intracellular domains, constitutively activate kinase phosphorylation and promote cell proliferation. More than 80% of patients with mastocytosis have the KITD816 V mutation, although other KIT mutations have been recently discovered [18].

Hoermann et al. evaluated the KITD816 V mutation burden by allele-specific oligonucleotide quantitative PCR (ASO-qPCR) and found that there was a higher mutation burden in patients with more advanced mastocytosis than in those with indolent disease [19]. Nevertheless, mutation burden did not correlate with tryptase levels or systemic symptoms, suggesting that the KITD816 V mutation is also present in non-mast cell hematopoietic lineage [19]. Moreover, using a cut-off of 2%, these authors were able to identify two prognostic groups that differ for median survival (not reached in < 2% vs. reached in 6–3 years in > 2%, respectively).

Other mutations involved in myeloid neoplasms have been detected in mast cells disorders, prevalently in ASM and SM-AHNMD, such as those involving the TET2, SRSF2, ASXL1 and RUNX1 genes and, rarely, the JAK2 and RAS genes [20]. While these mutations seem to confer a worse prognosis overall, the number of mutations involved in the so-called R/A/S panel (mutations of SRSF2/ASXL1/RUNX1) correlate with lower survival rate and clinical aggressiveness [21].

Bone marrow analyses should also include flow cytometry to evaluate CD2 and/or CD25 surface antigens; these molecules are not normally expressed by mast cells, and their presence identifies the neoplastic clone. Moreover, an aberrant expression of CD30 on neoplastic mast cells has been reported in about 80% of patients with indolent and aggressive SM [22]. As CD30 is not expressed on normal mast cells, interest in this molecule as a therapeutic target is increasing.

Radiological Tests

Complete skeletal X-ray, DXA and abdomen ultrasound should be performed in all patients to exclude early and/or asymptomatic bone, liver and spleen involvement. Endoscopy should be performed when symptoms of GI ulcer or persistent diarrhea are reported.

TREATMENT

As clinical situations vary, treatment options range from symptomatic drugs, such as with anti-H1 receptors, steroids and UV irradiation, all strategies prevalently used in patients with CM or ISM, to cytoreductive treatment in patients with more aggressive disease to control life-threatening symptoms or organ damage. Prognosis also widely differs among patients diagnosed with mastocytosis, with those with CM having an almost normal life expectancy and those with MCL having a median overall survival (OS) of < 1 year.

Symptomatic treatment

Anti-mediator agents, such as H1 and H2 antihistamines, anti-leukotriene drugs, proton pump inhibitors, cromolyn sodium and steroids, are almost always used to relieve the symptoms of mast cell activation. Nevertheless, some patients are severely limited in their daily activities, even with optimal management by symptomatic drugs. The authors of a recent placebo-controlled trial reported that masitinib, an oral kinase inhibitor, was well tolerated and effective in controlling at least one symptom of mastocytosis in patients presenting with pruritus, flushing, depression and fatigue, as assessed using standardized qualitative questionnaires [23]. Some authors have reported on omalizumab use among heavily treated patients resistant to two or more concomitant anti-mediator drugs [24]. Subcutaneous monthly administration of this humanized monoclonal antibody, which binds IgE and reduces its contact with mast cells and basophil surface receptors, showed an impressive control of symptoms

and rapid reduction of recurrent unexplained anaphylaxis [24].

Treatment with bisphosphonates should be promptly started in all patients presenting with low levels of vitamin D and radiological signs of osteoporosis, with the aim to reduce osteoclast activity and bone reabsorption [25].

Systemic Therapy

The first therapy for mastocytosis was interferon, which is also frequently used in the treatment of other myeloproliferative neoplasms for cytoreduction and disease burden control. Reported overall response rates (ORR) ranges from 20–30% up to 40%, with a variable duration of response and high rate of relapse after therapy withdrawal [18]. Lim et al. reported an ORR of 47 and 57% with and without associated steroids, respectively, and a median duration of response of 12 months [26].

Cladribine is a purine analog that can damage DNA even in diseases with low proliferative rate. The authors of a recent multicenter French study involving 68 patients with ISM and ASM reported an ORR of 72% (92% in ISM vs. 50% in ASM), even if no complete response was detected [27]. The median time between consecutive cladribine courses was 52 (range 28–83) days, the median duration of response was 3.7 years and the median OS was 8.2 years [27].

Since the discovery of the underlying KIT mutation, tyrosine kinase inhibitors (TKI) have been tested in the treatment of mastocytosis. Although imatinib, a small molecule kinase inhibitor, has been proven to inhibit transformed cells *in vitro*, almost all KIT mutations have shown resistance to imatinib *in vivo*. Imatinib has, however, been demonstrated to be effective *in vivo* in those rare patients with wild-type KIT mast cell diseases [28].

In a phase II study of monotherapy with dasatinib, an ORR of 33% was reported among 33 patients affected by SM, SM-AHD and MCL. Responses were durable, especially among ISM patients [29].

Midostaurin is an extremely potent TKI, that surpasses the resistance and inefficacy of other agents. A recent trial conducted among patients

with ASM, SM-AHD and MCL and measurable organ damage reported an ORR of 60% and a median OS of 33.9 months [31]. In particular, patients with ASM had an ORR of 75%, with a median duration of response and median OS not reached (95% confidence interval [CI] 24.1 months to not estimated, and 95% CI 28.7 months to not estimated). In patients with SM-AHNMD, the ORR was 58%, with a median duration of response of 12.7 (95% CI 7.4–31.4) months and median OS of 20.7 (95% CI 16.0–44.4) months. In patients with MCL, the ORR dropped to 50%, with a median duration of response not reached (95% CI 3.6 months to not estimated) and median OS of 9.4 months (95% CI 7.5 to not estimated) [30]. The authors of another study on 35 patients with ASM, SM-AHNMD and MCL reported an ORR of 51% and a median OS of 45 months from diagnosis, and identified a reduction in the c-KIT allele burden of > 25% to be predictive of better ORR and OS. Analyzing the number and characteristics of concomitant mutations, the same authors were able to demonstrate that all patients who progressed while on midostaurin therapy harbored a mutation in at least one gene of the S/A/R panel [31].

Chemotherapy regimens like those used in acute leukemia induction are the only valid therapeutic option for patients with MCL or progressing ASM to obtain a reduction of disease burden or a transient disease control before transplant procedure [32].

Hematopoietic Stem Cell Transplantation

Unfortunately, systemic treatments are not curative in patients with ASM. In refractory or rapidly progressing cases, hematopoietic stem cell transplantation may be an option in younger patients for whom a donor is available. However, data are still lacking, and determination of the optimum timing of the transplant procedure may be challenging, particularly among patients with less aggressive disease and partial response to therapy. In a recent retrospective analysis, Ustun and colleagues reported on the outcome of 57 patients with ASM, SM-AHNMD and MCL who received a transplant

from different donor sources after myeloablative and non-myeloablative condition regimens [33]. The ORR was 70% but the complete remission rate was only 28%; OS survival at 3 years was 57%, ranging from 74% in patients with SM-AHNMD to 17% in those with MCL [33].

New Drugs

A number of new drugs have been studied in recent years in *in vitro* experiments with mutated and wild-type KIT cellular lines [34]. Following the identification of CD30 expression on the surface of the neoplastic mast cell *in vitro* and among some patients with SM, the role of brentuximab-vedotin was evaluated. Although the authors of a little case series reported some durable response [35], the role of brentuximab-vedotin in the treatment of SM is still being debated.

A more promising drug is BLU-285, a highly selective inhibitor of KIT and platelet-derived growth factor receptor alpha (PDGFR α). The preliminary data on 12 patients with ASM show a marked reduction of disease burden, based on bone marrow infiltration, serum tryptase level and systemic symptoms [36]. Another KIT inhibitor, DCC-2618, has been reported to block mast cell growth and proliferation of the neoplastic non-mast cell marrow compartment in ASM and SM-AHNMD patients [37]. Both compounds are being tested in ongoing clinical trials.

RESPONSE CRITERIA

Defining global response criteria for mastocytosis remains a challenge due to the diverse clinical presentations of this condition. The therapeutic goal in treating the cutaneous and indolent forms of mastocytosis is the control of mediator release; in more the aggressive forms, ASM and MCL, the burden of disease needs to be reduced in order to prevent irreversible events, such as fracture, and restore organ function.

In 2003, Valent et al. proposed three categories of response [38]. Major responses defined

undetectable mast cell infiltration with no organomegaly and reduced tryptase levels; reduction of mast cell infiltration with reduced organomegaly and reduced tryptase levels; or clinical improvement of C findings without any decrease in mast cell burden and tryptase levels. Partial responses defined two categories consisting of < 50% reduction and > 50% reduction, respectively, of one or more C finding without progression. No response defined stable disease or progression in one or more C finding, even with improvement of other parameters [38]. Although these categories started to standardize the evaluation of response, the selected criteria were not always exhaustive for mastocytosis overall and did not help to predict clinical evolution.

The Mayo Clinic group published a more comprehensive evaluation of response in 2007. This group proposed differentiating response criteria of CM/ISM and ASM, taking into consideration the reduction of skin involvement, the duration of resolution of mediator-related symptoms and improvement of organomegaly for both categories and the extent of organ damage and infiltration of bone marrow for ASM only [39]. Moreover, significant duration of responses, improvement of bone disease and general symptoms (ascites, hypoalbuminemia, weight loss) and load of supportive transfusion are still difficult to quantify [40].

INVASIVE PROCEDURES

Anesthesia can be concern for patients and physicians alike: drug administration, change in the room temperature and physical stimuli or emotional stress related to the procedure itself are all considered to be triggers for anaphylaxis. On the other hand, published reports describe 6% and 0.4% of hypersensitivity events during general versus local or epidural anesthesia, respectively [41]. Anaphylactic reactions following radiocontrast media are not higher in patients with mastocytosis than in the general population [42]. Delivery is reported to be a low-risk procedure of anaphylaxis, except for some allergic symptoms complicating 11% of pregnancies [43].

The decision to administer peri-operative prophylaxis with steroids and anti-H1 receptor drugs should be targeted to a single patient. A history of anaphylaxis, drug allergy, triggers for flushing and emotional distress should all be considered. Gently contact to patient, Control of room temperature and benzodiazepine administration may also be helpful to the peri-operative management of patients [42].

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