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Update on Diagnosis and Treatment of Mastocytosis

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Abstract Mastocytosis is a disorder characterized by increased numbers of mast cells in tissues. Recent clinical observations highlight the association of mastocytosis with an increased risk of anaphylaxis and underline the diversity of this disease. At the molecular level, recent studies have attempted to unravel specific gene expression profiles for activating *c-kit* mutations in the etiology of mastocytosis. The diagnosis may be facilitated by surrogate markers and detection of aberrant immunophenotypic surface markers. New therapeutic strategies are in development based on intracellular signal pathways, or on application of topical treatments, as are novel forms of cytoreductive therapy, including tyrosine kinase inhibitors.

Keywords Mastocytosis · Mast cell activation syndrome · Anaphylaxis · Prognosis · KIT mutation · Diagnosis · Therapy · Treatment

Introduction

Mastocytosis is defined by an excessive number of mast cells in characteristic distribution predominantly in the skin, bone marrow, gastrointestinal tract, liver, spleen, and lymph nodes [1]. In children, mast cell hyperplasia is normally restricted to the skin (cutaneous mastocytosis), whereas in adults, it is also commonly found in extracutaneous organs (systemic mastocytosis). Systemic mastocytosis is classified into indolent systemic mastocytosis, mastocytosis with an associated hematologic disorder, aggressive systemic mastocytosis, mast cell leukemia, mast cell sarcoma, and extracutaneous mastocytoma [2]. The prognosis depends primarily on the degree of organ infiltration by mast cells, the evolution of associated hematologic disorders, occurrence of anaphylaxis, and associated osteoporosis with pathological fractures. Most recent studies and reports have focused on the increased risk and therapy for patients with mastocytosis for anaphylaxis, but also on the pathoetiology of the disease and the development of new therapeutic approaches.

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Mastocytosis and Anaphylaxis

In adults with mastocytosis, the cumulative prevalence of anaphylaxis has been reported to be 22% to 49%, and in children 6% to 9% [3•, 4•]. Those with systemic disease have an increased risk of anaphylaxis as compared with patients with cutaneous disease only [3•]. Patients with a history of anaphylaxis have higher basal serum tryptase levels than those without anaphylaxis. In children, the risk is restricted to those with extensive skin involvement and high serum tryptase levels [3•].

As in patients without mastocytosis, the most frequently reported elicitors of anaphylaxis are insect venoms, drugs, and food [3•, 4•]. Specific IgE antibodies are commonly found in patients with insect venom allergy, but not so against drugs and food. Severe and fatal reactions to hymenoptera venom have been described in patients with mastocytosis. In a few cases with urticaria pigmentosa and hymenoptera venom anaphylaxis, no sensitization could be detected by routine skin test and determination of specific IgE antibodies. In those patients, a basophil activation test

has proven to be a useful complementary diagnostic tool. Among patients with mastocytosis in one study, 9 of 11 with demonstrable specific serum IgE and 3 of 7 without had a positive basophil activation test [5]. Among 379 patients with a prior systemic immediate hypersensitivity reaction to a hymenoptera sting, 44 had an increased serum basal tryptase level greater than 11.4 ng/mL [6••]. Among the 34 patients who underwent a bone marrow analysis, the diagnosis was indolent systemic mastocytosis in 61.7%, and monoclonal mast cell activation syndrome in 26.5%. From this study, it was concluded that the concomitant presence of systemic reactions after hymenoptera stings and increased serum basal tryptase levels is a strong indication for a bone marrow examination in the diagnosis of clonal mast cell disease.

A fatal anaphylaxis was recently reported after a wasp sting in a patient with mastocytosis without prior evidence of insect venom allergy [7]. This raises the issue of a preventive allergen-specific immunotherapy in patients with mastocytosis.

Patients with mastocytosis may develop anaphylaxis not only in response to bee and wasp stings, but also after mosquito stings and stings of *Hippobosca equina*, such as was reported in one patient [8].

A variety of drugs have been reported to elicit anaphylaxis in patients with mastocytosis. Every year, reports have been published regarding patients with mastocytosis in whom the diagnosis of systemic mastocytosis was made following anaphylaxis to muscle relaxants or other drugs used during general anesthesia [9]. Other medications leading to reactions in patients with mastocytosis are opiates (including morphine and codeine), acetylsalicylic acid, other NSAIDs, antibiotics, and radiocontrast media [3•, 4•]. In a study of 137 individuals with drug- or food-induced anaphylaxis, only 9 (6.6%) had an increased basal tryptase level greater than 11.4 ng/mL, and only 2 patients (1.5%) were diagnosed with mastocytosis [10]. Thus, the association of clonal mast cell disorders with hymenoptera allergy seems to be much closer as compared with food- or drug-induced systemic reactions.

Foods have been implicated in the onset of anaphylactic episodes by some patients with mastocytosis; however, these cases only rarely have been confirmed by following clinical evaluation. Specific IgE to relevant foods is seldom found [4•]. The only "food" more commonly described to be associated with anaphylaxis in patients with mastocytosis is ethanol. The hypothesis that histamine intolerance may be responsible for anaphylaxis in patients with mastocytosis has not been supported by the observation that diamine oxidase levels were no different in patients with mastocytosis and without anaphylaxis [3•]. However, patients do report that factors such as exercise, heat, and consumption of alcohol in combination with food may elicit anaphylaxis such as was described in one patient developing anaphylaxis after ingestion of acetylsalicylic acid in combination with carrots [11]. In one study, 26% of anaphylactic reactions were reported to have developed after a combination of elicitors [3•]. In some patients with mastocytosis, anaphylaxis remains idiopathic despite an extensive search for elicitors.

The intensity of anaphylaxis in patients with mastocytosis has been described to be particularly severe. Among 55 patients with insect sting allergy and confirmed mastocytosis, 81% experienced severe anaphylaxis with shock or cardiopulmonary arrest [12]. In another study in which the severity of anaphylaxis was rated, 60% of patients reported severe symptoms and 43% experienced loss of consciousness [3•]. Fatal reactions may occur [7]. This is in agreement with the observation that baseline serum tryptase levels are the best-known predictor of the severity of anaphylaxis in insect sting–allergic patients [13•].

Other Clinical Manifestations of Mastocytosis

Symptoms of mastocytosis typically involve the skin (pruritus, urtication, flushing) and gastrointestinal tract (nausea, diarrhea, abdominal pain) [14]. In addition, the risk of developing severe osteoporosis is increased in patients with systemic mastocytosis, which is described regularly in the literature (eg, in the case of two young males developing vertebral fractures as a result of bone marrow mastocytosis) [15]. In a study of 75 patients with systemic mastocytosis who underwent skeletal x-rays and bone mineral density assessment, 31% had osteoporosis, 17% had vertebral fractures, 8% had osteosclerosis, and 11% suffered other forms of bone involvement [16].

Prognosis

Recent reports have studied the prognosis of mastocytosis in pregnancy, in adults, and in those with onset in childhood [17]. H_1-antihistamine agents may be indicated in pregnant patients with mastocytosis. Antihistamines were used most commonly, followed by oral prednisone [18]. Medications used during delivery were well-tolerated and included epidural analgesics. Although a subset of patients showed exacerbations of mastocytosis during and after pregnancy, labor and delivery progressed normally. Infants were born healthy and without mastocytosis.

Although the literature indicates that childhood-onset mastocytosis often may go into remission, hard data concerning the long-term prognosis of the disease are scarce. A recent study attempted to re-examine 17 individuals who had been diagnosed with mastocytosis as children 20 years earlier [19]. Fifteen patients were

successfully contacted, and there was complete regression in 67% of them, major regression in 20%, and partial regression of disease in 13%. Bone marrow examinations in three patients with persistent disease documented systemic mastocytosis with bone marrow involvement. Thus, initial bone marrow biopsies were prognostic for persistent disease.

In adults, the prognosis of indolent systemic mastocytosis is generally good, and in approximately 10% of the patients who have systemic mastocytosis for more than 10 years, urticaria pigmentosa may even regress [20]. In a study of 145 consecutive adult patients observed for a median of 147 months (range, 61–329 months), only 5 (3%) showed progression to a more aggressive form of the disease (aggressive systemic mastocytosis; systemic mastocytosis with an associated hematologic, non–mast cell lineage disease; or mast cell leukemia) [21••]. Multivariate analysis showed that serum β2-microglobulin, together with the presence of stem cell factor receptor gene *c-kit* mutation in mast cells plus myeloid and lymphoid hematopoietic lineages was the best combination of independent parameters for predicting disease progression. A prognosis concerning overall survival was negatively affected by an age younger than 60 years and development of associated clonal, hematologic, non–mast cell disorders, with a cumulative lethality of 2.2% at 5 years and 11% at 25 years.

Molecular Mechanisms of Disease

Mastocytosis is associated with an activating point mutation of the *c-kit* gene, the gene for KIT, the transmembrane receptor protein with tyrosine kinase activity for the ligand stem cell factor (the main growth factor for mast cells). Whereas this D816V activating mutation in codon 816, exon 17 of the gene can be found in more than 95% of adult patients with systemic mastocytosis, the frequency of mutations in pediatric mastocytosis is controversial. One new study analyzing the entire *c-kit* sequence from cutaneous biopsies of 50 children with mastocytosis found somatic activating mutations in *c-kit* in codon 816 in 42% and outside exon 17 in 44% [22]. A clear phenotype–genotype correlation, however, could not be demonstrated.

Several studies addressed the effect of D816V mutations on the signal transduction pathway. When the biologic effects of the D816V mutation in the phosphotransferase domain were compared with those in the extracellular domain after introduction into rodent Ba/F3, EML, Rat2, and human TF-1 cells, both mutations induced receptor autophosphorylation and both activated the signal transducer and activator of transcription (STAT)-signaling pathway, whereas Akt was only activated by extracellular domain mutations [23]. In two neoplastic mast cell lines, P815 and HMC-1 with a D816V mutant kit, STAT1, STAT3, and STAT5 proteins were activated downstream of the KIT D816 mutant, but only STAT5 was transcriptionally active in these cells [24]. When the expression of phosphorylated STAT5 (pSTAT5) in neoplastic mast cells and systemic mastocytosis was studied by immunohistochemistry, neoplastic mast cells were found to display pSTAT5 in all 40 systemic mastocytosis patients examined when Ba/F3 cells with doxycycline-inducible expression of KIT D816V were used [25]. Induction of KIT D816V resulted in an increased expression of pSTAT5 without a substantial increase in total STAT5. The tyrosine kinase inhibitor PKC412 was found to counteract the expression of pSTAT5, and a dominant negative STAT5 construct was found to inhibit the growth of HMC-1 cells. The authors concluded that neoplastic mast cells express pSTAT5, KIT D816V promotes STAT5 activation, and STAT5 activation contributes to the growth of neoplastic mast cells.

In search of interactive genetic events contributing to the phenotypic diversity of KIT D816V–positive systemic mastocytosis, gene expression profiles were analyzed in 22 patients with indolent systemic mastocytosis—12 of whom had a history of insect venom allergy and 10 of whom were without a history of anaphylaxis—and in 43 healthy controls. This was done by whole genome gene expression analysis of RNA samples isolated from the peripheral blood [26, 27]. Comparison of gene expression indicated that the main pathways in which the differentially expressed genes are involved are ubiquitin-mediated proteolysis, mitogen-activated protein kinase signal pathway, pathways in cancer, and Janus kinase–STAT signaling [26]. In patients with indolent systemic mastocytosis, gene expression profiles were reported to differ between those with and those without a history of insect venom allergy [27]. In one study, 44 patients with KIT D816V–positive systemic mastocytosis were evaluated for coexisting *NRAS*, *KRAS*, *HRAS*, and *MRAS* mutations [28]. Activating *MRAS* mutations were identified in only two of eight patients with advanced disease, but not in patients with indolent systemic mastocytosis. KIT D816V was not detected in bone marrow mast cell progenitors, which indicates that *NRAS* mutations may have the potential to precede KIT D816V in clonal development.

Diagnosis of Mastocytosis and Mast Cell Activation Disorders

The European Union/US consensus group defined criteria for the classification of systemic mastocytosis in 2001 that were adopted by the World Health Organization in 2001 and 2008. In a letter to *Blood*, it was suggested to eliminate mast cell leukemia and systemic mastocytosis with an associated clonal, hematologic, non–mast cell lineage

disorder from the list and to place smoldering systemic mastocytosis as a separate category [29], but this was rebuked by the European Competence Network on Mastocytosis with the main argument that the KIT D816V mutation and other aberrant phenotype expressions, including CD30, represent the basis for the disease [30]. According to currently accepted guidelines, the diagnosis of systemic mastocytosis requires the major criterion "multifocal clusters of mast cells" with at least one minor criterion, or three minor criteria, as listed in Table 1. Patients with mastocytosis often have symptoms related to excessive mast cell mediator release. In one study, patients with systemic mastocytosis had a significant increase in urinary leukotriene E_4 excretion in comparison to a control group of patients [31]. From this study, it has been concluded that leukotriene E_4 excretion can be used as a surrogate marker that potentially contributes to clinical symptoms.

Mastocytosis is considered in the differential diagnosis of idiopathic anaphylaxis. In one study, 12 patients with idiopathic anaphylaxis were analyzed for the presence of major or minor criteria for mastocytosis [32•]. Whereas no demonstrable tissue increase in mast cells was found, 5 of 12 patients met minor criteria for mast cell disease, such as the D816V KIT mutation in mast cells enriched from bone marrow, aberrant expression of CD25 in bone marrow aspirates, or increased basal serum tryptase levels. The conclusion of the study was that clonal mast cell disease may be present in some patients with idiopathic anaphylaxis. In addition, the term *monoclonal mast cell activation syndrome* has been proposed for patients who had anaphylaxis-like symptoms and one or more markers of clonal mast cell disease but no diagnosis of systemic mastocytosis [2]. In addition, there is an attempt to define a diagnosis, or at this stage rather a checkpoint of mast cell activation syndrome, in patients with clinical signs of repeated mast cell activation [33]. Proposed diagnostic criteria include symptoms of mast cell mediator release; an improvement after mast cell anti-mediator therapy with antihistamines, anti-leukotrienes, or mast cell blockers; and evidence of an increase in specific surrogate marker for mast cell activation during an attack, such as tryptase, histamine (metabolites), or prostaglandin F_2. However, this is only after exclusion of primary (mastocytosis, monoclonal mast cell activation syndrome) and secondary disorders of mast cell activation (allergic disorders, physical urticaria, mast cell activation in autoimmune or chronic inflammatory disorders, autoimmune urticaria), and of the idiopathic entities of anaphylaxis, angioedema, and urticaria. A consensus document by the European Network of Mastocytosis has been submitted by Valent et al.

In a recent study, 83 patients with clinical symptoms attributable to mast cell mediator release in the absence of mastocytosis-associated skin lesions were analyzed for the presence of clonal mast cell disease and clinical symptomatology [34•]. By demonstration of the D816V KIT mutation in cell sorting–purified populations of different bone marrow cells and immunophenotypical analysis of CD25 expression, clonality was demonstrated in 51 patients, with the majority fulfilling the criteria for systemic mastocytosis (n=48). Although the remaining 32 patients with symptoms of mast cell activation but without clonality also presented with idiopathic and allergen-induced anaphylaxis, they clinically differed from patients with clonal disease. In the former, the most common triggers for acute episodes were more often drugs and less often insect stings; the clinical presentation of anaphylaxis was more often urticaria, angioedema, and dyspnea and less often presyncopy and syncopy; patients were predominantly female; and serum tryptase levels were lower as compared with patients with clonal mast cell disease presenting as systemic mastocytosis (Table 2). A probability score indicating the presence of clonal mastocytosis based on gender, absence of urticaria, presence of presyncopy or syncopy, and serum tryptase levels greater than 25 ng/mL was proposed, and it was concluded that patients with a high score should undergo bone marrow biopsy and aspirate analysis for the suspicion of systemic mastocytosis, even in the absence of skin lesions.

Following this study, the frequency of bone marrow mastocytosis without skin involvement was analyzed in one study center [35]. In 99 consecutive patients with indolent

Table 1 Diagnosis of systemic mastocytosis based on World Health Organization criteria

Major criterion
Multifocal dense infiltrates of mast cells in bone marrow and/or other extracutaneous tissues
Minor criteria
1. More than 25% of the mast cells in bone marrow smears or tissue biopsy sections are spindle shaped or display atypical morphology
2. Detection of a *c-kit* point mutation in codon 816 in blood, bone marrow, or other lesional tissue
3. Mast cells in the bone marrow, blood, or other lesional tissue express CD25 or CD2
4. Baseline total tryptase level is persistently >20 ng/mL

One major and one minor, or three minor criteria are needed for the diagnosis of systemic mastocytosis
(*Adapted from* Valent et al. [2])

Table 2 Differences between patients with indolent systemic mastocytosis and no skin involvement and those with nonclonal mast cell activation symptoms

Parameter	Indolent systemic mastocytosis	Nonclonal mast cell activation symptom
Patients, *N*	48	32
Elicitors of systemic symptoms, *n*		
Insect stings	27	7
Drugs	5	11
Food	2	4
Idiopathic or other	14	18
Clinical symptoms, *estimated%*		
Urticaria	37	78
Angioedema	4	60
Dyspnea	40	72
Presyncope	77	40
Syncope	77	40
Serum basal tryptase, *ng/mL*	25.2	15.4
Males, *n* (%)	35 (73)	10 (31)

(*Adapted from* Alvarez-Twose et al. [34•])

systemic mastocytosis, skin involvement was documented in 51 patients in this center, whereas 46 patients presented only with bone marrow mastocytosis. In more than 95% of cases with isolated bone marrow mastocytosis, a bone marrow examination was performed because of anaphylaxis. These patients were predominantly male and had a lower bone marrow mast cell burden and less elevated tryptase levels than patients with skin involvement. The authors of this study concluded that bone marrow mastocytosis may not be as rare as previously believed.

In patients with systemic mastocytosis, different molecular and prognostic subtypes were analyzed by flow cytometry for their immunophenotypical markers [36]. By analyzing bone marrow samples from 123 patients with systemic mastocytosis and 92 controls, 3 clearly different maturation-associated monophenotypic profiles were found. Bone marrow mast cells from patients with aggressive systemic mastocytosis and mast cell leukemia showed an immature phenotype with clonal involvement of all myeloid lineages with the D816V KIT mutation; aberrant positivity for CD25 (usually in the absence of CD2); decreased expression of CD117, FcεRI, and *HLA-I*; and increased positivity for CD123, *HLA-DQ*, and *HLA-DR*, reflecting a more immature mast cell phenotype. A second group of patients with indolent systemic mastocytosis and clonal mast cell activation disorders showed a phenotypic profile similar to that of activated mature mast cells, expressing CD25, CD2, FcεRI, CD63, CD69, and CD203c activation markers. A third group with a form of indolent systemic mastocytosis not carrying the D816V KIT mutation showed a phenotype of normal resting mature bone marrow mast cells with strong expression of CD117 and FcεRI, but lacking CD25, CD2, CD63, and CD203c activation markers. The study concluded that the determination of immunophenotypic patterns may help determine the prognosis of patients with systemic mastocytosis by grouping them into those with a poor prognosis (when finding an immature immunophenotypic expression) and those with a good prognosis (when a mature activated or resting phenotype is found).

Therapy

Therapy for Cutaneous and Indolent Systemic Mastocytosis

There is no effective causal therapy for mastocytosis at the present time, as treatment is symptomatic (Fig. 1) [37]. In cutaneous and indolent systemic mastocytosis, aggressive forms of therapy are not indicated. Patients should be informed about the disease, the prognosis, and possible complications. Therapy for mastocytosis includes avoidance of trigger factors, targeting symptoms of mast cell mediator release, and therapy for skin lesions. Adults with mastocytosis and children with bullous lesions and more severe involvement are at increased risk of anaphylaxis and should carry an emergency kit for self-medication that includes epinephrine and, as warranted, antihistamine and a corticosteroid. General anesthesia is risky for patients with mastocytosis, and the anesthetist must be informed. If precautions are taken, at least in children, severe anaphylaxis is uncommon. This was shown in a study of 22 children with mastocytosis, in whom 24 anesthetic procedures with general anaesthesia were well-tolerated, with the exception of 2 cases with

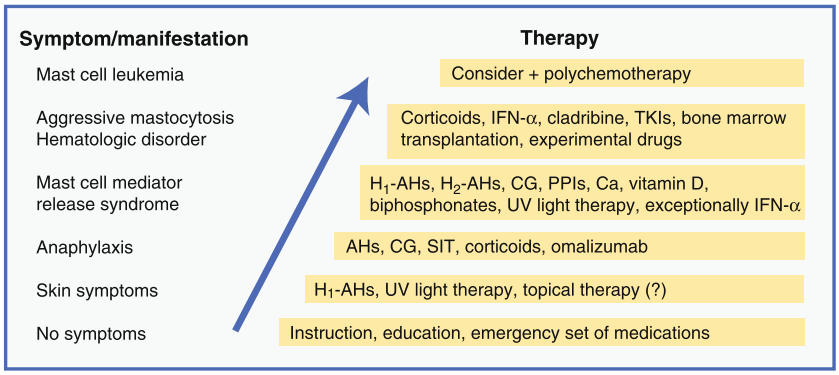

Fig. 1 Overview of therapy for mastocytosis. AH—antihistamine; Ca—calcium; CG—cromoglycate; IFN—interferon; PPI—proton pump inhibitor; SIT—specific immunotherapy; TKI—tyrosine kinase inhibitor

flushing and 4 cases with nausea and/or vomiting, even in the absence of specific premedication [38].

Allergen-specific immunotherapy should be administered in patients with hymenoptera venom allergy. Although the risk of adverse reactions and treatment failure is somewhat increased, most patients with mastocytosis are protected following this approach [39]. In light of previous fatal cases of anaphylaxis following discontinuation of treatment in patients with mastocytosis, lifelong allergen-specific immunotherapy is recommended.

Treatment with omalizumab (anti-IgE) continues to be successful in selected patients with otherwise uncontrolled idiopathic anaphylaxis and in those with anaphylaxis during the initiation of specific immunotherapy [40, 41].

The first-line therapy for patients with mastocytosis and idiopathic anaphylaxis, however, and that for patients with pruritus and associated wheal and flare of skin lesions is nonsedating H_1-antihistamines. For prophylaxis of recurrent episodes of anaphylaxis or persistent pruritus, antihistamines should be administered daily. In vitro antihistamines have been shown to inhibit spontaneous growth of neoplastic mast cell lines [42]. Whether this also affects in vivo neoplastic mast cell growth remains to be determined.

Treatment with histamine receptor blockers, proton pump inhibitors, anticholinergics, or cromolyn sodium may be administered as needed. Calcium and vitamin D are prescribed in osteopenia and biphosphonates in case of osteoporosis. In patients with predominantly gastrointestinal symptoms but also with symptoms of musculoskeletal pain, fatigue, and headache, therapy with oral and inhaled sodium cromolyn may be tried, as noted in a case report [43]. An exploratory study in 20 allergic and 40 nonallergic individuals in whom aqueous cream containing sodium cromoglycate was applied before skin prick test with allergens, codeine, and histamine suggests that this medication may be effective in reducing pruritus [44]. In another trial, the lipid raft modulator miltefosine showed a trend toward reducing the volume of wheals in 39 adult patients with skin involvement of mastocytosis after topical therapy [45], but it cannot yet be recommended.

Application of UV light therapy has been reported to lead to dermatologic improvement in patients with cutaneous mastocytosis. Application of UVA1 as well as psoralen plus UVA (PUVA) therapy and narrow-band UVB phototherapy has been reported to reduce pruritus and urtication [46, 47]. However, it must be considered that relapse typically occurs a few months after therapy is discontinued, and that these forms of therapy must be weighed against the potential for inducing side effects. It is well-known that topical corticosteroids are also effective [48]; however, due to the potential for side effects, they should be used primarily for the treatment of localized skin lesions such as mastocytomas causing flushing or blistering.

Therapy for Aggressive Forms of Mastocytosis

In patients with aggressive systemic mastocytosis and slow progression, interferon-α or the purine nucleoside analogue cladribine is the first-line treatment, sometimes initially in combination with prednisolone [2, 49]. If cladribine fails, polychemotherapy, palliative cytoreduction with hydroxyurea, and hematopoietic stem cell transplantation are the treatments of choice [21••, 50]. Patients with systemic mastocytosis and associated hematologic, non–mast cell lineage disease should be treated in the same way as other patients with this hematologic disease. Novel approaches have been proposed for the treatment of patients with aggressive systemic mastocytosis and mast cell leukemia: new tyrosine kinase inhibitors under clinical investigation for blocking KIT are dasatinib and PKC412 (midostaurin). Unfortunately, dasatinib has yielded largely disappointing results in clinical trials together with a serious side effect profile. PKC412 is currently being tested in clinical trials. However, long-lasting effects have not been described. Further experimental drugs under investigation are the kinase inhibitors masitinib and bafetinib, as well as the mTOR (mammalian target of rapamycin)

inhibitor everolimus and phosphatidylinositol 3-kinase blockers. Thus, treatment of advanced systemic mastocytosis remains a challenge. First- and second-line therapies may provide some good, albeit transient responses, and new approaches are in development with the hope of achieving stable, long-term remissions.

Conclusions

Mastocytosis has been extensively studied during the past few years. Two of the most important insights are that mastocytosis and elevation of basal tryptase levels are risk factors for anaphylaxis, and that anaphylaxis can occur with monoclonal mast cells as a basis for the disease. The term *mast cell activation syndrome* is on the way to being defined for symptoms of mast cell mediator release in which other established diagnoses of primary or secondary mast cell disorders or known idiopathic entities are not met. The prognosis for patients with mastocytosis is generally good and can be predicted by the clonal involvement of multiple hematologic lineages with the D816V *kit* mutation, and by an immature phenotype of bone marrow mast cells. Molecular mechanisms of disease are analyzed, and new therapeutic approaches are in development that may provide better control of aggressive forms of mastocytosis in the future.

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