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Anaphylaxis (P Lieberman, Section Editor)

Diagnosis and Treatment of Anaphylaxis in Patients with Mastocytosis

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Opinion statement

Patients with systemic mastocytosis (SM) have an increased risk for the development of severe, life-threatening anaphylactic episodes. Despite prophylactic therapy with anti-mediator-type drugs, a mast cell (MC) activation syndrome (MCAS) may be diagnosed in these patients. In a subset of them, an immunoglobulin (Ig)E-dependent allergy is detected as underlying disease. The severity and frequency of anaphylactic reactions neither correlate with the burden of neoplastic MCs nor with specific IgE levels or the serum tryptase level. However, the 'event-related' increase in serum tryptase is usually indicative of a severe reaction. In addition, there is a positive correlation between severe anaphylaxis and the type of allergen in SM. In fact, many of these MCAS patients suffer from bee or wasp venom allergy. Currently recommended standard treatments for anaphylaxis in mastocytosis include the prophylactic use of histamine receptor (HR) antagonists, MC stabilizers, life-long immunotherapy in hymenoptera venom allergic patients, and epinephrine injections for emergency situations. In those who have an excessive burden of MCs (smouldering or aggressive SM) cladribine (2CdA) may be effective and may reduce the frequency of severe life-threatening events, and the same can sometimes be achieved with interferon-alpha (IFNα). In the future, additional treatment options, such as IgE-depletion or administration

of tyrosine kinase inhibitors targeting IgE-dependent mediator secretion as well as KIT activation and thus MC expansion, may become standard therapy.

Key points

1. Patients with mastocytosis have a high risk of developing severe anaphylaxis, especially when suffering from hymenoptera venom allergy, but sometimes also even in the absence of any known trigger or allergy.
2. Management of anaphylaxis in mastocytosis requires special considerations and special knowledge about potential triggers, disease pathogenesis, and treatment options and should be performed in, or in collaboration with, a specialized center.

Introduction

Mastocytosis is a term collectively used for a rare and heterogeneous group of neoplasms characterized by abnormal expansion and accumulation of mast cells (MCs) in one or more organs [1–6]. Traditionally, mastocytosis is divided into pure cutaneous mastocytosis (CM) and systemic mast-cell disorders, also referred to as systemic mastocytosis (SM). The cutaneous form of the disease usually develops in (early) childhood, and in general has a favorable prognosis. In many cases, skin lesions resolve spontaneously during or after puberty. SM is usually diagnosed in adulthood and is characterized by internal organ involvement [1–6]. In most patients with SM, the bone marrow contains diagnostic aggregates of atypical neoplastic MCs [1–6]. Skin lesions may or may not be detectable in SM. The *KIT* mutation D816V is found in clonal cells in most patients [7–11]. Neoplastic MCs in SM typically display the adhesion-receptor LFA-2 (CD2) and the interleukin (IL)-2 receptor alpha chain (CD25) [1–6, 12–15]. The basal serum tryptase level is usually elevated (>20 ng/mL) [3–6, 16–18]. The following entities of SM have been defined by the World Health Organization (WHO): indolent systemic mastocytosis (ISM), SM with associated clonal hematologic non-MC-lineage disease, aggressive SM (ASM), and MC leukemia [19–23]. The smouldering variant of SM (SSM), defined by an extensive burden of MCs, was initially listed as a provisional sub-category of ISM [19, 20]. However, more recently, SSM has been recognized as a unique and separate SM category [21, 24]. Table 1 shows the current classification of mastocytosis.

Regardless of the variant of SM, the release of various pro-inflammatory and/or vasoactive mediators from MCs can cause diverse clinical problems [21, 25–27, 28•, 29•, 30]. The symptoms recorded vary in severity and frequency, and range from mild pruritus or flushing and headache to severe hypotension or even life-threatening anaphylaxis [21, 25–27, 28•, 29•, 30]. In severe cases, tryptase levels increase substantially and an MC activation syndrome (MCAS) is often diagnosed [31, 32••, 33]. In some of these patients, a co-existing allergy is demonstrable [25–27, 28•, 29•, 30] (Table 2). In other patients, however, the etiology and triggering factors remain obscure. Therapy with anti-mediator-type drugs, MC stabilizers, epinephrine, and glucocorticosteroids is often sufficient to bring the symptoms of anaphylaxis under control [25–27, 28•, 29•, 30, 31, 32••, 33]. For those with a proven immunoglobulin (Ig)E-dependent (type I) allergy, immunotherapy may be a helpful approach, especially when hymenoptera allergy is diagnosed. In addition, strict avoidance of all known triggering factors is essential to prolong symptom-free intervals [25–27, 28•, 29•, 30]. However, in some of these cases, severe, life-threatening events occur despite anti-mediator-type treatment, immunotherapy, and prevention. For these cases it is quite difficult to establish a satisfactory treatment plan.

Table 1. Consensus classification of mastocytosis[a]

Cutaneous mastocytosis (CM)
Maculopapular CM (MPCM) = urticaria pigmentosa (UP)
Diffuse CM (DCM)
Mastocytoma of skin (solitary mastocytoma of skin)
Systemic mastocytosis (SM)
Indolent SM (ISM)
Smouldering SM (SSM)[b]
SM with associated clonal hematologic non-mast cell lineage disease (SM-AHNMD)
Aggressive SM (ASM)
Mast-cell leukemia (MCL)
Extracutaneous mastocytoma
Mast cell sarcoma

[a]The consensus classification reflects the WHO classification 2008
[b]Extending the current WHO classification, SSM is now recognized as a separate category of SM

The risk of severe anaphylaxis (MCAS) in mastocytosis

In about 10–20 % of all patients with SM, at least one severe life-threatening anaphylactic event is documented in their lifetime. As mentioned, some of these patients have an IgE-dependent allergy and MCAS [25–27, 28•, 29•, 30]. The type and severity of these reactions differ greatly among patients. So far, little is known about the mechanisms and triggering factors underlying the severity of MCAS and the hyper-responsiveness of MCs in these patients. Recent studies have revealed a potential relationship between symptom severity and certain genetic constellations in patients with SM [34]. A rare genetic predisposition for an increased tryptase level and an increased frequency of mediator-related events has also been described [35]. So far, it remains unknown whether the same genetic patterns are also relevant in SM. There are also data supporting a relationship between an elevated tryptase level and an increased risk of severe anaphylaxis in indolent SM [36]. In other studies, however, severe anaphylaxis occurred preferentially in patients with a low burden of neoplastic MCs or did not correlate with tryptase levels [28•, 29•, 30, 31, 37, 38]. A generally accepted risk factor for recurrent severe anaphylaxis in SM is a known allergy against hymenoptera venom. In fact, various studies have shown that venom allergic patients with SM have a particularly high risk for developing severe, life-threatening anaphylactic events after hymenoptera stings [39–44].

It has also been suggested that a chronically activated KIT receptor may be responsible for the hyper-reactivity of MCs in SM. In fact, in almost all patients with SM, neoplastic MCs exhibit the activating *KIT* point-mutation

Table 2. Conditions and factors known to provoke anaphylaxis in patients with mastocytosis

Condition/Factor[a]	Known or suggested mechanism(s)
Insect (hymenoptera) venom	IgE-dependent allergy
Microbes (bacteria, viruses, others)	Direct effects on mast cells
Food	Food allergies (rare)
Pollen and other plant allergens	IgE-dependent allergy (rare cause of anaphylaxis)
Stress	Nerve–mast-cell interactions
Cold or hot temperatures	Temperature effect on mast cells
Aspirin	Idiosyncrasy, Syk activation
Other drugs	Allergy or direct effects on mast cells
Alcohol	Direct effect on mast cells
Toxins	Direct effects on mast cells

[a]Most of these conditions/factors can induce anaphylactic events also in allergic (susceptible) patients in the absence of mastocytosis

D816V, which is considered to contribute essentially to the autonomous growth and expansion of neoplastic MCs in these patients [6–10, 45]. The D816V mutant has been implicated in hyper-reactivity of MCs in SM because the KIT ligand stem cell factor (SCF) reportedly augments IgE-dependent mediator release in normal MCs [46–48]. However, in a substantial number of patients with SM, no mediator-related symptoms are recorded even if the burden of neoplastic MCs is huge, which would argue against a role of KIT D816V in the releasability of MCs. Moreover, recent data suggest that KIT D816V does not lead to an IgE-mediated hyper-responsiveness when transfected into human MCs [49].

Grading of mediator-related symptoms and anaphylaxis in mastocytosis

A number of different grading systems for anaphylaxis have been established, such as the 'Müller Scale', which is widely used in patients with insect venom allergy [50]. This score is also useful to grade anaphylaxis in patients with MC disorders. In 2007, the EU-US consensus group presented a grading system adjusted to symptoms recorded in patients with mastocytosis [21]. Based on this grading system, the following categories of patients are defined: grade 0 (no symptoms), grade 1 (no therapy required), grade 2 (moderate, kept under control with anti-mediator therapy), grade 3 (not sufficiently controlled with drug therapy) and grade 4 (symptoms require hospitalization) [21]. The frequency of grade 4 is further divided into A (<1/year), B (>1/year and <1/month), and C (>1/month) [21]. Severe hypotension and MCAS (usually grade 4) may occur in any category of SM and also in CM patients without (histologic) evidence of systemic disease. It is noteworthy that, allergens as well as allergen-specific IgE can be identified as specific triggers of anaphylaxis in some of these patients [25–27, 28•, 29•, 30]. Accordingly, anaphylaxis in mastocytosis is divided into cases with (+) or without (–) proven IgE-dependency of the anaphylactic reaction [21].

Mast cell activation syndromes (MCAS)

MCAS is a syndrome characterized by severe, episodic, systemic symptoms, with proven involvement of MCs and MC-derived mediators [31, 32••, 51–55]. It is noteworthy that MCAS is not a novel category of mastocytosis, but a clinical syndrome that can develop in any type of mastocytosis and in any kind of patients, and can also disappear even if mastocytosis is still detectable. The diagnosis of MCAS can be established when (a) severe recurrent MC activation, usually in form of anaphylaxis, is found; (b) involvement of MCs can be demonstrated, preferably by a tryptase test (increase in serum tryptase during or shortly after the event); and (c) the symptoms respond to treatment with anti-mediator-type drugs or MC-stabilizing drugs [31, 32••]. The diagnostic elevation of tryptase is defined as at least 20 % of baseline plus absolute 2 ng/mL [32••]. For example, an increase from 10 ng/mL basal to >14 ng/mL at the event is diagnostic (10+2 [20 %]+2=14). It is important to collect serum samples for basal tryptase at the time of the event as well as at least 2 days after complete resolution of all symptoms. In patients in whom the basal tryptase level is elevated, an underlying MC disease has to be considered [21, 31, 32••].

In several patients, only one or two of the above-outlined criteria of MCAS can be documented because mediators were not recorded (e.g., assay not available) or the patient was not responsive to anti-mediator-type or MC-stabilizing agents. In other patients, serum tryptase levels are not found to be increased. Sometimes, other MC-derived mediators, like histamine, urinary histamine metabolites or prostaglandin D2, can be measured and show a diagnostic elevation during anaphylaxis [56–59]. Finally, MC activation can also manifest as a less severe condition, so that MCAS cannot be diagnosed, even if these patients are suffering from quite a lot of symptoms requiring therapy. In other words, not all mediator-related and clinically relevant symptoms are (can be) classified as MCAS. It should also be mentioned that basophil activation can lead to severe symptoms mimicking MC activation or even MCAS. In those in whom MC activation is documented, further investigations are considered in order to detect or rule out the presence of a clonal MC disorder [31, 32••]. In patients in whom mastocytosis (CM or SM) is detected as an underlying disease, the presence of clinically relevant signs of MC activation requiring therapy is indicated by the diagnostic label 'SY' added as a subscript to the diagnosis (e.g., SM_{SY}) [21]. Nevertheless, not all patients labeled as SM_{SY} are suffering from an overt MCAS [21, 32••].

Underlying disorders and classification of MCAS

As mentioned above, MCAS often develops on the basis of an underlying (reactive) disease, such as an IgE-dependent allergy or an auto-immune disease (without mastocytosis) but also in association with a neoplastic MC disease = mastocytosis [21, 31, 32••, 33–35, 51–55] (Table 3). Notably, MCAS can occur in any category of CM and SM. Based on the underlying condition (disease), MCAS can be divided into primary MCAS,

secondary MCAS, and an idiopathic MCAS variant [31, 32••, 52] (Table 3). In patients with primary MCAS, a clonal *KIT*-mutated population of MCs is found. The related condition may be CM or SM, depending on documented criteria [31, 32••, 52]. However, even in the absence of a full-blown mastocytosis, the diagnosis of a primary MCAS can be established. In such cases, monoclonal MCs are detected, but only one or two minor SM criteria regarding clonality of MCs (i.e., c-kit D816V mutation and/or CD25 expression) can be recorded, so that the diagnosis SM cannot be established formally [31, 32••, 52] (Table 3). In these patients, the follow-up may reveal the development of an overt CM or SM. Most patients with secondary MCAS are diagnosed with an IgE-dependent allergy [31, 32••, 51–55]. If neither an allergy (or another reactive disease) nor a clonal MC population (*KIT*-mutated) can be documented, a diagnosis of 'idiopathic MCAS' can be established (Table 3). However, the number of cases with idiopathic MCAS is expected to decrease as the knowledge about underlying conditions and improved diagnostic markers and algorithms increase.

Prophylactic therapy and immunotherapy

In many patients with CM or SM, anaphylactic reactions are followed by a symptom-free interval. In other patients, mediator-related symptoms are mild but persistent in the event-free interval. In some cases, the triggering factors (e.g., an allergen) are known. In many other patients, however, the triggering agent (or situation) provoking an anaphylactic reaction remains undefined. For those patients who have successfully identified their triggering factors, the most important aspect of the management is to avoid all agents and all situations that may provoke an event [21, 25–27, 32••]. In addition, it is standard to recommend prophylactic anti-mediator type drugs for all patients with mastocytosis (CM or SM) with chronic or frequent mast cell activation symptoms. These mediator-targeting drugs are prescribed according to published algorithms [21, 25–27, 32••]. The basis of treatment remains a combination of histamine receptor type 1 (HR1) blockers with or without HR2 blockers [21, 25–27, 32••]. In high-risk situations (e.g., prior to surgery or chemotherapy), glucocorticosteroids and/or extra doses of HR1

Table 3. Classification of mast cell activation syndromes *(MCAS)*

Variant of MCAS	Clinical and laboratory findings
Primary	Clonal mast cells found
	a) Established SM: criteria to diagnose SM are fulfilled[a]
	b) Established CM: criteria for CM are fulfilled but the criteria to diagnose SM are not fulfilled
	c) Neither CM nor SM can be diagnosed, but one or both of the following minor SM criteria documenting mast-cell clonality found: (i) *KIT* D816V or (ii) CD25 expression in mast cells
Secondary	An underlying allergic, atopic, inflammatory or neoplastic disease is found but no monoclonal mast cells are detectable (wt *KIT* and CD25 expression in mast cells not found)
Idiopathic	No underlying allergy or atopy and no monoclonal (*KIT*-mutated or CD25+) mast cells are detectable

SM systemic mastocytosis, *CM* cutaneous mastocytosis

[a] The diagnosis of SM is established when at least one major and one minor SM criterion or at least three minor SM criteria are met

blockers (usually IV) are often administered. In patients with mastocytosis in whom an IgE-dependent allergy against hymenoptera venom has been detected, life-long immunotherapy should be performed with recognition of potential side effects, such as increased prevalence of local or systemic allergic reactions [60–63]. In patients with inhalant allergies and symptoms of allergic rhinitis, the safety and efficacy of immunotherapy has not been systemically studied, but the risk-versus-benefit ratio is generally not considered to be favorable to warrant inhalant immunotherapy, and the treatment plan has to be based on the individual situation in each case. A summary of prophylactic anti-mediator-type therapies is shown in Table 4. All patients with mastocytosis should be advised to carry two or three epinephrine self-injectors and to use them in emergency situations according to prescribed instructions.

Mast-cell-stabilizing agents

A number of MC-stabilizing agents have been proposed for the treatment of patients with mastocytosis. These agents include, among others, glucocorticosteroids, aspirin, cromolyn sodium, ketotifen, and cyclosporine-A (CSA) [63–73] (Table 5). Most of these drugs can suppress activation of normal (mouse, rodent or/and human) MCs, and it is assumed that these drugs also block mediator production and/or release in clonal MCs in patients with SM. Glucocorticosteroids may exert a number of additional beneficial effects on MCs. Likewise, glucocorticosteroids have been described to block the synthesis of SCF (a major regulator of MC growth, survival, and activation) in fibroblasts and other tissue-fixed cells [74]. Aspirin has also been considered for the treatment of severe anaphylactic reactions in SM [69, 71]. Indeed, aspirin may suppress the generation of prostaglandin D2

Table 4. Prophylactic therapy in patients with mastocytosis

Recommended treatment	Specific indication
Histamine receptor type 1 blocker	All patients
Histamine receptor type 2 blocker	Patients with gastrointestinal symptoms or those not responding to H1 antihistamines alone
Glucocorticosteroids	Premedication before high-risk situations[a]
	Preventive maintenance therapy at low doses for recurrent frequent anaphylactic reactions not responsive to histamine receptor blockers
Immunotherapy	Hymenoptera venom allergy[b]
Cladribine (2CdA)	SM with high mast-cell burden (SSM) and severe, recurrent, life-threatening anaphylaxis[c]

SM systemic mastocytosis, *SSM* smoldering SM

[a]Examples: premedication prior to surgery or administration after a bee or wasp sting to prevent biphasic or late reactions; however, even in high-risk patients, glucocorticosteroids should not be prescribed routinely and only with great caution and with recognition that long-term treatment is associated with systemic side effects including the risk of severe osteopathy in SM

[b]In patients with SM in whom a hymenoptera venom allergy is detected, life-long immunotherapy is usually recommended if tolerated

[c] Cladribine should usually be administered only to patients with aggressive SM or mast-cell leukemia. However, in select patients with SSM and a very high risk of life-threatening anaphylaxis, the administration of cladribine may also be justified

Table 5. Mast cell-stabilizing and other immunoregulatory drugs used to treat symptoms in patients with mastocytosis

Drug	Proposed mechanism(s) of action
Glucocorticosteroids	Blocks mediator production and cytokine synthesis as well as mediator secretion in mast cells; multiple additional effects, including suppression of SCF production in local tissue cells in various organs
Cromolyn sodium	Effects on various cells types, including mast cells, may block IgE-dependent activation of mast cells
Ketotifen	Inhibits activation of mast cells, inhibits binding of histamine to HR1 receptors
Cyclosporine-A	Inhibits production of mediators and cytokines in mast cells as well as mast-cell activation and mediator release

HR1 histamine receptor type 1, *IgE* immunoglobulin E, *SCF* stem cell factor

(PGD2) in human MCs. However, the doses of aspirin required to clinically suppress MC activation and PGD2 synthesis are rather high (0.5–1.0 g/day). On the other hand, aspirin may provoke gastrointestinal problems (like bleeding). Furthermore, aspirin may induce severe hypotension (anaphylaxis) via multiple mechanisms, including idiosyncratic reactions and Syk activation (Table 2) [75–78]. Therefore, aspirin should only be administered in select cases and with great caution in those SM patients whose tolerance to aspirin and NSAIDs are known. Cromolyn sodium and ketotifen are often used in patients who are resistant against HR1 or HR2 blockers and glucocorticosteroids [63, 64, 67–69]. However, both drugs also produce side effects and may not suppress all mediator-related symptoms in all patients. Cromolyn sodium is frequently prescribed in patients with gastrointestinal problems and resistance against HR2 blockers. In these patients, the addition of a proton pump inhibitor (PPI) may also be helpful. CSA reportedly exerts an inhibitory effect on IgE-dependent activation of human MCs [79–81]. However, treatment with CSA is associated with immunosuppression and other adverse effects such as renal toxicity and hypertension as well as the risk of opportunistic infections and development of secondary tumors or tumor progression. Therefore, CSA and other similar immunosuppressive agents are not prescribed routinely in patients with SM. In this regard it has to be mentioned that indolent SM is a premalignant condition that exhibits a low but measurable potential for malignant progression. An interesting aspect is that some of the HR blockers, such as loratidine and desloratidine, can also block growth and thus mediator production in neoplastic MCs *in vitro* [82]. However, it remains unknown whether this effect also occurs *in vivo* in patients with mastocytosis. Another important aspect is that combination treatment with multiple anti-mediator-type drugs is often helpful. Likewise, combinations of HR1 and HR2 blockers are often prescribed successfully in patients with SM. However, there are also several pitfalls that need to be avoided. One typical error is to switch a mastocytosis patient from an HR2 blocker to a PPI because of a 'poor response' to the HR2-targeting drug. Whereas the combination is often helpful in these patients, discontinuation of the HR2 blocker may worsen the MC activation symptoms despite the use of a PPI.

Novel treatment concepts

Usually, cytoreductive drugs should not be prescribed for treatment of mediator-related symptoms because of the potential risks. However, in SM_{SY} patients (MCAS) with a high MC burden, typically seen in patients with SSM or ASM, cytoreductive therapy should be considered. Indeed, it has been reported that in SSM patients with MCAS, the frequency of recurrent life-threatening anaphylaxis events declines substantially after treatment with cladribine (2CdA) [28•, 83, 84]. A new potent type of MC-targeting drugs are tyrosine kinase inhibitors (TKIs), such as imatinib, PKC412 (midostaurin), dasatinib or masitinib (Table 6) [85–93]. Some of these TKIs, like PKC412, block KIT D816V activation and thus MC proliferation in patients with SM [88–91]. However, KIT D816V is resistant against most of the other TKIs, including imatinib and masitinib. An interesting aspect is that dasatinib and PKC412 not only block KIT-dependent MC proliferation but also inhibit IgE-dependent (allergen-induced) activation and mediator secretion in MC in *in vitro* studies [94, 95], although dasatinib has a dose-dependent dual role which may augment MC activation in lower doses (Table 6). Therefore, TKIs like PKC412 are considered as emerging and promising agents for patients with advanced SM, SM_{SY}, and MCAS. Another emerging treatment approach in patients with mastocytosis and secondary IgE-dependent MCAS may be IgE depletion. In fact, it has been described in anecdotal cases that IgE depletion with omalizumab is effective in suppressing the symptoms of anaphylaxis in such patients [96–99]. However, omalizumab itself can cause anaphylaxis, and no data from controlled clinical trials are available. It also remains unknown whether continuous treatment with omalizumab can indeed extend the event-free interval in these patients.

Table 6. Effects of KIT tyrosine kinase inhibitors (TKI) on growth and IgE-dependent secretion of histamine

Drug	Major targets	Inhibits growth of MC[a]		Inhibits IgE-dependent histamine release[b]
		KIT_{wt} [a]	KIT_{D816V}	
Imatinib	KIT, PDGFR	+	–	–
Midostaurin	KIT, SYK, PKC	+	+	+
Masitinib	KIT, LYN, FYN	+	–	+/–c
Nilotinib	KIT, PDGFR	+	+/–	–
Dasatinib	KIT, BTK, SRC	+	+	+/–d
Bosutinib	SRC, TEC, BTK	+/–	–	–
Ponatinib	KIT, SRC, LCK	+	+/–	–

MC mast cells, *IgE* immunoglobulin E, *wt* wild type, *PDGFR* platelet-derived growth factor

[a]Imatinib and masitinib may also suppress the growth of neoplastic MC in rare forms of systemic mastocytosis associated with (very) rare KIT mutations: K509I, F522C, D816T, D840N

[b]Most data have been collected in in vitro assays with human basophils or mast cells

[c]Masitinib inhibits IgE-dependent mast-cell degranulation at high concentrations

[d]At low concentrations of dasatinib, the drug even augments IgE-dependent mediator secretion from mast cells and basophils, whereas at high concentrations, dasatinib can completely suppress IgE-dependent histamine release. Because of the short half-life of dasatinib, the augmenting effects may be more relevant in vivo

Response evaluation

Response evaluation should be adjusted to the type and severity of symptoms recorded in patients with mastocytosis. According to a proposal of the EU-US consensus group, responses to anti-mediator-type drugs are classified as (i) complete response (complete resolution of symptoms), (ii) a major response (>50 % reduction in severity and/or significant decrease in frequency of events: B→A or C→B), (iii) a partial response (10–50 % reduction in severity; no major decrease in frequency), and (iv) no response (<10 % reduction; no decrease in frequency) [32••].

Concluding remarks and future perspectives

Patients with mastocytosis are at risk for the development of severe anaphylaxis and MCAS. In the past few years, several new concepts around mechanisms and triggering factors underlying MC activation in these patients have emerged. In addition, novel treatment concepts have been proposed and new targeted drugs suppressing MC activation and/or MC proliferation in SM have been developed and are currently being tested in clinical trials. Whether these drugs can completely suppress MCAS reactions in patients with mastocytosis remains to be determined in clinical trials.

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Compliance with Ethics Guidelines

Conflict of Interest

Peter Valent is a consultant for a global Novartis trial examining the effects of PKC412, and received honoraria and a research grant from Novartis and BMS.
Cem Akin is a consultant for a global Novartis trial examining the effects of PKC412 in advanced SM.
Michel Arock declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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