

Drug-induced mast cell eradication: A novel approach to treat mast cell activation disorders?



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Mast cell (MC) activation is a key event in allergic reactions, other inflammatory states, and MC activation syndromes. MC-stabilizing agents, mediator-targeting drugs, and drugs interfering with mediator effects are often prescribed for these patients. However, the clinical efficacy of these drugs varies depending on the numbers of involved MCs and the underlying pathology. One straightforward approach would be to eradicate the primary target cell. To date however, no MC-eradicating treatment approach has been developed for patients with MC activation disorders. Nevertheless, recent data suggest that long-term treatment with agents effectively inhibiting KIT function results in the virtual eradication of tissue MCs and a sustained decrease in serum tryptase levels. In many of these patients, MC depletion is associated with a substantial improvement in mediator-induced symptoms. In patients with an underlying KIT D816V-positive mastocytosis, such MC eradication requires an effective inhibitor of KIT D816V, such as avapritinib. However, the use of KIT inhibitors must be balanced against their potential side effects. Here we discuss

MC-eradicating strategies in various disease models, the feasibility of this approach, available clinical data, and future prospects for the use of KIT-targeting drugs in MC activation disorders. (*J Allergy Clin Immunol* 2022;149:1866-74.)

Key words: Mast cells, KIT, Mast cell activation syndrome, tyrosine kinase inhibitor, midostaurin, avapritinib

Mast cells (MCs) are key effector cells of allergic reactions and other inflammatory processes in various pathologic conditions.¹⁻⁴ These cells display high-affinity IgE receptors, also known as FcεRI, as well as many other activation-linked surface antigens and receptors, such as C5aR or MRGPRX2, and they store an array of vasoactive and inflammation-triggering mediators in their metachromatic granules.¹⁻⁴ During an anaphylactic reaction, allergen-induced cross-linking of MC FcεRI results in the release of preformed granule-stored mediators, including various proteases, histamine, and newly synthesized chemokines and

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Abbreviations used

MC: Mast cell
MCAS: Mast cell activation syndrome
SCF: Stem cell factor
SM: Systemic mastocytosis
TKI: Tyrosine kinase inhibitor
WT: Wild-type

cytokines.¹⁻⁴ In addition, activated MCs release lipid membrane-derived arachidonic acid metabolites.¹⁻⁴

MCs originate from multilineage hematopoietic stem and progenitor cells as well as from MC-committed progenitors.⁴⁻⁹ These stem and progenitor cells reside in the bone marrow but are also detected in the peripheral blood and in extramedullary organs.⁴⁻¹¹ A complex network of cytokines and growth factor receptors is involved in regulating the differentiation, maturation, migration, adhesion, homing, and activation of MCs in health and disease.⁴⁻¹² The key regulator of the development, survival, and function of MCs is stem cell factor (SCF) acting through its receptor, KIT. KIT itself is expressed on the surface of uncommitted stem cells, MC progenitor cells, and mature MCs,⁴⁻¹² but it is also expressed on a number of other cell types, including melanocytes, Cajal cells of the gastrointestinal tract, and germ cells.^{13,14}

MC activation occurs in a number of different pathologic conditions and disorders, including allergic diseases, chronic inflammatory reactions, infectious diseases, intolerance reactions, and toxic reactions.^{1-4,15-20} In patients with allergic (atopic) disorders and in those with mastocytosis, MC activation may be substantial and systemic, often resulting in overt anaphylaxis.^{4,15,16-19} When the symptoms are severe, episodic, and recurrent, a MC activation syndrome (MCAS) may be diagnosed.^{15,18-21} In some of these cases, life-threatening anaphylaxis is seen, especially when 1 or more underlying conditions and contributing pathologies, such as a concomitant mastocytosis and/or allergy, are also present.^{15,18-21}

Based on mouse studies, symptoms typically recorded in an anaphylactic (allergen-induced and IgE-dependent) reaction are largely if not entirely dependent on the presence of MCs.²²⁻²⁶ Basophils also can participate in anaphylactic reactions, but their contribution to the manifestations of severe anaphylaxis is assumed to be generally of less impact. Thus, MCs are a critical target cell population in anaphylactic reactions in various disease models, including IgE-dependent allergies, mastocytosis, and MCAS.

In patients with severe forms of MC activation and anaphylaxis, a number of drugs are used in the hope of bringing MC activation under control.²⁷⁻³² In the acute phase of an MC activation-related event (anaphylactic shock), "emergency drugs" such as epinephrine (first-line immediate therapy) and corticosteroids, as well as antihistamines are administered.²⁷⁻²⁹ In the symptom-free interval, MC-stabilizing agents, mediator-targeting drugs, and drugs interfering with the effects of these mediators on various target cells (eg, histamine receptor blocker) are prescribed to help prevent or lessen an episode of recurrent anaphylaxis, should it occur.^{27,28,30-32}

In certain forms of MC activation, anaphylactic events may be life-threatening and resistant to conventional therapy.^{15-19,27-30} These include events in patients with an underlying MC neoplasm (mastocytosis), an underlying genetic predisposition, an atopic

diathesis, and/or multiple severe IgE-dependent allergies. When 2 or 3 of these conditions are present in the same patient, the risk for recurrent life-threatening events may be exceptionally high.¹⁵⁻²¹ In such cases a MCAS may be diagnosed.^{15,19-21} For patients with recurrent severe events, including those with MCAS not protected by conventional approaches, additional pharmacologic agents, including IgE-targeting antibodies (omalizumab), specific immunotherapy, and/or MC-stabilizing agents, may be administered.³³⁻³⁸

An emerging novel strategy is to reduce the numbers of MCs in the hope of decreasing or even eliminating the risk of occurrence of severe anaphylaxis. Especially in patients with both MCAS and systemic mastocytosis (SM), where the numbers of MCs are excessively elevated, a reduction in or eradication of MC could be a highly effective therapeutic maneuver. In support of such an approach, several studies have shown that MC reduction induced by an effective inhibitor of KIT D816V or other drugs with similar effects on MCs is followed by a decrease in the symptom burden and an improvement in quality of life.³⁹⁻⁴⁴ Indeed, KIT, a tyrosine kinase receptor for SCF, is a well-known master regulator of MCs and their progenitor cells,^{10,11,13} and the KIT mutant form D816V has recently been identified as a primary target in MC-dependent disorders.³⁹ Currently however, the approach of targeting KIT and thus suppressing MC development with a highly effective pharmacologic inhibitor is offered almost exclusively to patients with advanced SM.³⁹⁻⁴⁴ On the other hand, there are a few studies in which the efficacy of KIT-targeting drugs in indolent SM has been explored with the goal of suppressing MC growth and MC activation.

Such experience prompts our discussion of the potential use of established and novel KIT-targeting drugs as MC-eradicating therapy in patients with anaphylaxis and MCAS, particularly in the context of IgE-dependent allergies, atopic and other predisposing conditions, and SM. Moreover, we review the available data and discuss future applications in clinical trials, as well as associated concerns related to safety, side effects, and special indications.

ROLE OF KIT IN EXPANSION AND ACTIVATION OF MCs

Human and mouse MCs reportedly derive from transplantable hematopoietic stem and progenitor cells.⁴⁵⁻⁴⁷ The tyrosine kinase receptor KIT and its ligand, SCF, also called KIT ligand, play a dominant role in the development and maturation of tissue MCs.⁹⁻¹¹ In contrast to other myeloid cells, MCs are long-lived. This is because the development of fully mature MCs from their stem cells and pluripotent and committed MC progenitor cells may take several months.^{4-6,9,48-53} In addition, some mature tissue MCs survive months or perhaps years when residing within local tissue microenvironments. According to observations in patients with clonal MC disorders who have undergone hematopoietic stem cell transplantation, the *in vivo* development of human MCs from donor stem cells takes at least 6 months.⁴⁷ Similarly, full differentiation of human MCs from their stem and progenitor cells and full maturation *in vitro* takes at least 6 to 12 weeks.^{6,48-53} At maturation, MCs reside in local tissue sites at which SCF and other growth factors and cytokines are expressed, supporting long-term survival as well as effector cell functions. It is important to note that the survival of mature MCs in various tissues is dependent on SCF and KIT and that after an effective blockade of the SCF-KIT axis *in vivo*, it takes at least several weeks

TABLE I. Molecular targets and activity profiles of KIT-targeting TKIs

Drug/name	KIT-blocking profile	Additional major targets	Blocks <i>in vitro</i> growth of		Blocks MC activation*
			Normal MCs	KIT-mutated MCs	
Imatinib	WT KIT, a few mutant forms	ABL1, ABL2, PDGFRs, many more	+	—	±
Masitinib	WT KIT, a few mutant forms	LYN	nk	—	±
Dasatinib	WT KIT, a few mutant forms (KIT D816V) [†]	ABL1, ABL2, BTK, PDGFRs, many more	+ [†]	± [†]	+
Nilotinib	WT KIT, a few mutant forms (KIT D816V)	ABL1, ABL2,	+	±	±
Midostaurin	WT KIT, most mutant forms, KIT D816V	FES, FGR, SYK, LYN, PDGFRs, many more	+	+	+
Avapritinib	WT KIT, most mutant forms, KIT D816V	PDGFRs	nk	+	±
Ripretinib	WT KIT, most mutant forms, KIT D816V	PDGFRs, VEGFR2	nk	+	±
Nintedanib	WT KIT, most mutant forms, KIT D816V	PDGFRs, VEGFR2	nk	+	±
Bezuclastinib	KIT D816V and other KIT mutant forms	FGFR	nk	nk	nk

BTK, Bruton tyrosine kinase; FGFR, fibroblast growth factor receptor; nk, not known; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

*All KIT-targeting drugs can suppress SCF-mediated (KIT-dependent) MC activation and SCF-induced mediator secretion, whereas only 2 of these drugs, midostaurin and dasatinib (both of which recognize IgE receptor downstream targets), also substantially block IgE-dependent mediator secretion in MCs. Plus sign indicates substantial suppression/blockage; plus or minus sign indicates some suppressing effects under certain conditions; and minus sign indicates that no suppression (not even with high drug concentrations) is seen.

[†]Although dasatinib blocks the activity of WT KIT and KIT D816V and is capable of suppressing the *in vitro* growth and differentiation of human MCs, it is usually unable to block the expansion of KIT D816V-positive neoplastic MCs in patients with mastocytosis, which is due most probably to the low *in vivo* half-life (a few hours) of this drug.

until (normal) mature tissue MCs undergo apoptosis and disappear.^{10,11,47}

Other cytokines can also induce or promote MC differentiation. Whereas in the mouse and rat, several growth factors, including IL-3 and SCF, may induce MC development,^{2,9} differentiation of human MCs is promoted by only a few cytokines.⁴⁸⁻⁵⁶ In fact, in an early phase of MC development (at the stem and progenitor cell level), IL-3, IL-6, and IL-9 can promote proliferation and thus SCF-induced development of MCs.^{48,51-53} IL-4, in turn, acts on a more mature stage of MC development. In particular, IL-4 promotes *in vitro* maturation, chymase expression, and expression of FcεRI in maturing MC precursor cells cultured in the presence of SCF.⁵³⁻⁵⁶

CLASSES OF KIT-TARGETING TKIs, DRUG-TARGET INTERACTION PROFILES, AND PHARMACOLOGY

KIT-targeting tyrosine kinase inhibitors (TKIs) can essentially be divided into (1) drugs interacting with several different kinase targets, including wild-type (WT) KIT but not with KIT D816V (eg, imatinib), (2) drugs that interact primarily or selectively with WT KIT but not with KIT D816V or other kinase targets (eg, masitinib), (3) drugs that recognize WT KIT, KIT D816V, and several other oncogenic kinases (eg, midostaurin), and (4) inhibitors of KIT D816V (and sometimes WT KIT) that interact with only a limited number of additional kinase targets (eg, avapritinib). A compilation of such KIT-targeting drugs is provided in Table I.

In addition, several antibody-based drugs against KIT or the KIT ligand SCF, and several chimeric antigen receptor T-cell approaches using KIT as a cellular target, are currently being developed and tested in preclinical studies and clinical trials. In 1 study, the anti-KIT antibody CDX-0159 produced profound and

lasting MC suppression in healthy donors.⁵⁷ In addition, bispecific antibodies targeting KIT and other key surface targets have been developed. In this article however, our focus is on small molecule-type KIT TKIs, with more to follow as information accumulates on these other approaches targeting KIT-bearing cells.

Available KIT-targeting TKIs vary in their efficacy against KIT and KIT variants, their half-life *in vivo*, their effects on SCF-dependent and IgE-mediated MC activation, and their toxicity profiles. For example, although dasatinib inhibits WT KIT and exerts effects on KIT D816V and IgE-dependent mediator secretion and MC activation *in vitro*,⁵⁸⁻⁶⁰ the pharmacologic half-life of the drug (2-4 hours) is too limited to suppress KIT continuously and block MC growth and activation *in vivo*. Another important consideration is that depending on their structure and chemical properties, some KIT-targeting drugs are degraded *in vivo* into more or less inactive metabolites. For example, midostaurin is degraded into 2 major metabolites.⁶¹ Whereas both midostaurin metabolites continue to block SYK and thus anti-IgE-induced histamine release, only 1 of these metabolites can sufficiently block KIT and KIT downstream signaling, and thus SCF-induced or KIT D816V-mediated growth of MCs.⁶²

When a KIT TKI is applied in a routine setting or in clinical trials, a most important point to consider is that only a KIT TKI that can block KIT D816V (class 3 and 4 TKIs) will be able to suppress the development and survival of neoplastic MCs in patients with KIT D816V-positive SM. Another important point is that highly specific KIT-targeting drugs lack activity against other oncogenic kinases and FcεRI downstream signaling molecules. The consequence is that these agents may be able to counteract MC activation and MCAS to a substantial degree only when most or all of the MCs in a given patient have been eliminated.

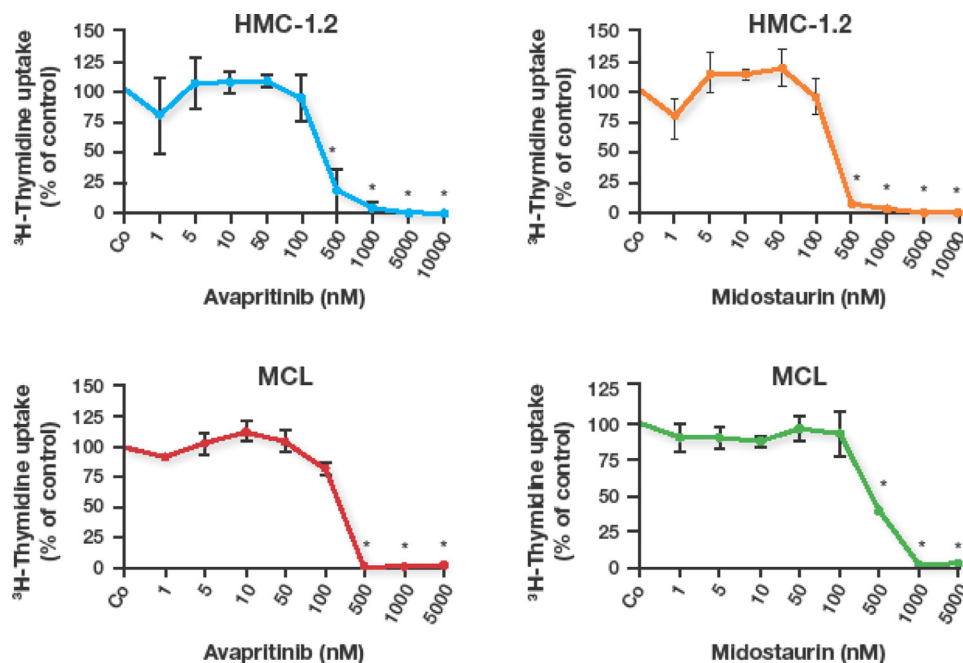


FIG 1. Effects of avapritinib and midostaurin on proliferation of neoplastic MCs. HMC-1.2 cells expressing KIT D816V (upper panels) and primary neoplastic MCs obtained from a patient with MC leukemia (MCL) (lower panels) were incubated in control medium or medium containing various concentrations of avapritinib (left panels) or midostaurin (right panels) at 37°C for 48 hours. Then, ³H-thymidine uptake was measured. Results are expressed as percentages of the control and represent the means ± SDs from 3 independent experiments (HMC-1.2) or triplicate experiments (MCL cells). The data are in line with those in the available literature,^{58,70,72,78} and they suggest that the effective range and values obtained with these cell lines for the concentration that inhibits 50% are within the plasma concentrations (nM range) measured in patients with mastocytosis who are receiving these drugs. **P* < .05 compared with the control.

It is also important to know that side effects correlate with the number and types of targets recognized and that most of these TKIs have been developed to treat malignant diseases (cancer) but not MCAS or anaphylaxis. Finally, because expression of KIT is not limited to MCs,^{13,14} consideration should also be given to the possibility of unknown adverse effects of administration of KIT TKIs over longer periods of time.

EFFECTS OF KIT-TARGETING TKIs ON DEVELOPMENT OF MCs FROM THEIR PROGENITORS

As mentioned, the development of normal and neoplastic MCs is largely dependent on a functionally active KIT receptor. In normal MCs, KIT activation is initiated by its ligand SCF.⁹⁻¹¹ In contrast, in neoplastic MCs, specific point mutations in *KIT* lead to SCF-independent activation of KIT and thus to autonomous (SCF-independent) differentiation of MCs from their stem and progenitor cells.^{63,64} In line with these observations, all 4 classes of KIT TKIs can inhibit SCF-induced growth of stem cells and thus SCF-dependent *in vitro* development of MCs from their normal stem and progenitor cells.⁶⁵⁻⁶⁸ In contrast, only drugs targeting KIT D816V can suppress the growth and survival of MCs and MC lines exhibiting *KIT* D816V, whereas these cells are resistant to imatinib, masitinib, or other drugs lacking activity against KIT D816V (Table I).⁶⁹⁻⁷³ Fig 1 shows the growth-inhibitory effects of avapritinib and midostaurin on neoplastic MCs exhibiting *KIT* D816V.

The same efficacy profiles are also observed in patients *in vivo*. In particular, drugs targeting only WT KIT but not KIT D816V (imatinib, masitinib, and others) are unable to suppress growth of neoplastic MCs in patients with KIT D816V–positive advanced SM.⁷⁴⁻⁷⁹ In contrast, drugs targeting KIT D816V, such as midostaurin or avapritinib, suppress expansion of MC counts in patients with advanced SM.^{39-44,78-80} For these patients, avapritinib appears to be a more effective agent.^{43,44} An associated observation is that administration of avapritinib leads to a rapid decrease in the burden of neoplastic MCs in these patients.^{43,44} This observation is best explained by the fact that this drug is a very effective inhibitor of KIT D816V and that not only proliferating immature progenitor cells but also mature MCs depend on KIT D816V for survival and thus represent a sensitive target.⁷²

Another remarkable phenomenon is that midostaurin induces rapid improvement of mediator-related symptoms in patients with advanced SM.⁴¹ This cannot be explained by a reduction of the MC burden alone, as MC numbers decrease only slowly (or not at all) with midostaurin.³⁹ Instead, this beneficial drug effect appears to be due to its impact on SYK activity in MCs and thus, on IgE-dependent and IgE-independent MC activation and mediator secretion.⁶² Indeed, even in patients without meaningful hematologic responses, midostaurin can alleviate mediator-induced symptoms and quality of life substantially.⁴¹ Moreover, in a phase II trial, midostaurin was able to improve refractory symptoms caused by MC mediator release and thus the quality of life in more than 70% of all patients with indolent systemic mastocytosis.⁸¹ At high concentrations, avapritinib also exerts some

TABLE II. Clinical efficacy profiles of KIT-targeting TKIs in SM

TKI name	Conditions for which it is approved by the FDA for	Complete eradication of MCs	Effects on mediator-induced symptoms	Recurrent and clinically relevant adverse events
Imatinib	SM without <i>KIT</i> D816V or unknown <i>KIT</i> mutation status	Seen in a few cases with WT <i>KIT</i> , <i>KIT</i> K5091, <i>KIT</i> F522C, or other <i>KIT</i> variants	Limited or no effects	Facial edema, skin depigmentation, obstipation, renal function impairment,* diarrhea
Midostaurin	Advanced SM	Seen in a few cases with <i>KIT</i> D816V-positive advanced SM	Major effects on mediator-related symptoms in most patients with advanced SM	Nausea, vomiting, diarrhea
Avapritinib	Advanced SM	Seen in 30%-40% of patients with <i>KIT</i> D816V-positive advanced SM [†]	Major effects on mediator-related symptoms in most patients with advanced SM	Cytopenia, facial edema, skin depigmentation, diarrhea, nausea, intracranial bleeding [‡]

FDA, US Food and Drug Administration.

*After several years of treatment, less than 5% of all patients with chronic myeloid leukemia develop an impairment in kidney function; in many of these patients, a renal disease is also detected.

[†]In about 30% of these patients, avapritinib also induced molecular remission, defined as no evidence of *KIT* D816V as determined by using droplet digital PCR.

[‡]Intracranial bleeding has been reported mostly in patients with severe thrombocytopenia.

inhibitory effects on MCs and on basophil activation and mediator release (Table I).

Finally, it must be noted that there are adult patients with SM whose neoplastic MCs do not exhibit KIT D816V but who have other mutant forms of KIT or even WT KIT.⁸²⁻⁸⁶ These include patients with well-differentiated SM, a subset of patients with MC leukemia (including MC leukemia arising from MC sarcoma), and some with aggressive SM.⁸²⁻⁸⁶ In these patients, KIT is often sensitive not only to midostaurin but also to imatinib or other WT KIT-targeting drugs (Table I).⁸²⁻⁸⁶ Therefore, imatinib may be considered as an MC-depleting therapy in such patients, especially in those with a well-differentiated MC morphology. Indeed, major responses or even remissions have been reported in these patients during imatinib therapy.⁸²⁻⁸⁶ It should also be noted that imatinib is a US Food and Drug Administration- and European Medicines Agency-approved drug for this indication (KIT D816V-negative SM).

WILL A POTENT KIT-TARGETING TKI ERADICATE NORMAL MCs?

To date, little is known about the ability of KIT-targeting drugs to reduce or even eradicate normal MCs and their progenitors in patients. In 1 report, patients with chronic myeloid leukemia were treated with imatinib for several years. During this therapy, the MC numbers in the bone marrow and serum tryptase levels were determined. The numbers of MCs decreased after 12 months; and after 24 months, MCs were almost completely absent in bone marrow sections.⁶⁸ Simultaneously, serum tryptase levels decreased to the point where they were low to undetectable.⁶⁸ These observations strongly suggest that a potent WT KIT inhibitor such as imatinib can eradicate normal MCs when administered for at least 24 months. In contrast, after 12 months MCs decreased in number but were still detectable.⁶⁸ Whether this is due to the relatively weak effect of imatinib on nondividing mature MCs (having a lifetime of several months *in vivo*) and/or to the fact that imatinib preferentially blocks the growth of (dividing) MC progenitors remains at present unknown. In several of the patients with chronic myeloid leukemia who were examined, allergy-related symptoms also decreased or disappeared

and patients were able to limit or stop antiallergic drugs (P.V., unpublished observation).

CAN A POTENT KIT D816V-TARGETING TKI INDUCE MC ERADICATION IN SM?

Several promising TKIs targeting KIT D816V have recently been developed, and many more may be developed in the near future. Available TKIs at the time of writing of this review include midostaurin, ripretinib, avapritinib, BLU-263, bezuglastinib, and nintedanib.^{39-44,70-73,87} Midostaurin and avapritinib, in particular, have been rapidly developed and translated into clinical applications.³⁹⁻⁴⁴ Their clinical efficacy is summarized in Table II. Interestingly, these 2 drugs behave differentially in patients with KIT D816V-positive advanced SM. Midostaurin blocks MC activation by interfering with KIT-dependent and IgE-dependent signaling pathways in neoplastic MCs⁶² and exhibits some MC-reducing ability in most patients with KIT D816V-positive advanced SM, but midostaurin is usually unable to eliminate all neoplastic MCs in patients.^{39,40} In contrast, avapritinib is often able to induce substantial MC cyto-reduction, and thus hematologic remission, in a substantial subset of patients with advanced KIT D816V-positive SM,^{43,44} and at higher concentrations, it also shows some inhibitory effects on IgE-dependent MC activation (Table I). Whether this additional effect of avapritinib can explain the rapid clinical improvement sometimes seen in patients with MC disorders⁸⁸ remains at present unknown.

In summary, both midostaurin and avapritinib are highly effective in reducing the symptoms of MC activation in patients with advanced SM, but the primary mechanisms of drug action appear to vary, and only avapritinib may qualify as a drug inducing MC eradication in a subset of patients with advanced SM. Fig 2 shows target organs that may be affected by mastocytosis and/or MCAS.

EFFECTS OF KIT-TARGETING TKIs ON SCF-DEPENDENT AND IgE-DEPENDENT MEDIATOR SECRETION IN MCs

The releasability of MCs depends on a number of different factors, such as the type of allergen, numbers of IgE receptors, and

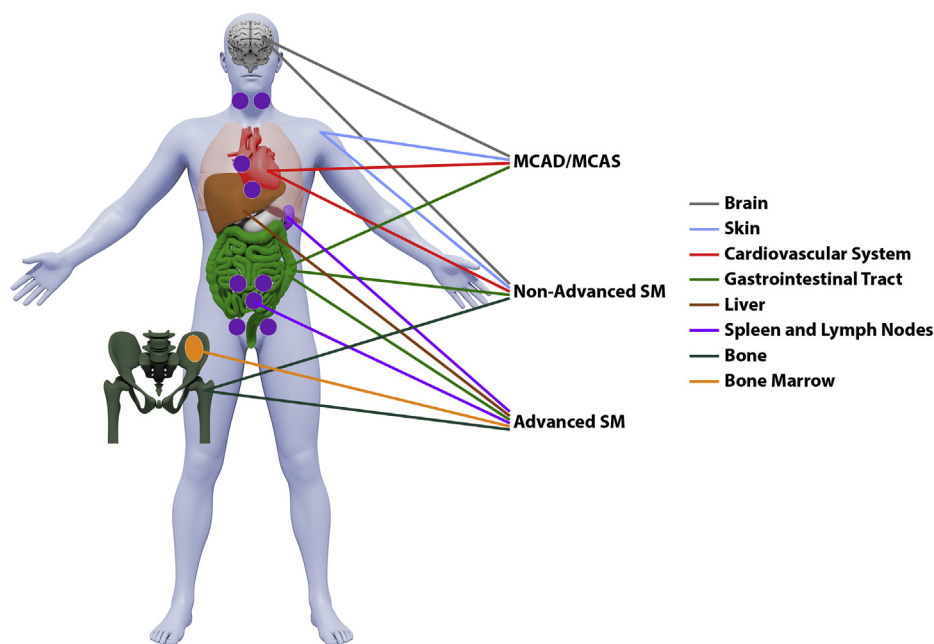


FIG 2. Target organs primarily involved in mastocytosis and MCAS. Several different organ systems may be involved in patients with MCAS, nonadvanced SM, and advanced SM. Whereas in patients with MCAS and nonadvanced SM, MC-derived mediators usually affect organ function (eg, anaphylaxis, skin rash, ulcerative disease in the gastrointestinal tract), patients with advanced SM often suffer from organ damage induced by the local MC infiltrates (typical examples are severe cytopenia, hepatosplenomegaly with ascites and weight loss, and focal osteolysis). *MCAD*, MC activation disorder.

cytokine exposure. For example, IL-4 can promote the expression of high-affinity IgE-binding sites on MCs,^{54,56,89} and SCF can augment releasability in MCs stimulated by IgE-dependent or IgE-independent stimuli.⁹⁰⁻⁹³ At higher concentrations and with prolonged exposure, SCF itself is capable of inducing mediator secretion in MCs through activation of KIT.⁹⁰⁻⁹³ Therefore, potent KIT inhibitors or antibodies against KIT may be able to block SCF-induced MC activation and possibly SCF-augmented (priming) effects on IgE-dependent MC activation (Table 1). However, these effects of KIT TKIs may be negligible in clinical (*in vivo*) contexts. Rather, MC activation induced by exogenous antigens (allergens) is usually not effectively blocked by pharmacologically meaningful concentrations of a specific inhibitor of WT KIT or KIT D816V.

In KIT D816V-positive MCs in patients with SM, the situation is similar. Here, SCF is no longer required to activate KIT, as KIT is activated in an autonomous manner⁶³ and the affected cells appear to be chronically activated and possibly desensitized against KIT-dependent stimuli. Therefore, KIT inhibitors may be capable of interfering with MC activation only when these drugs are also directed against other critical targets relevant in IgE-dependent and/or KIT-dependent MC activation, such as SYK, LYN, or BTK (Table 1).⁶² Indeed, midostaurin has been reported to suppress IgE-dependent activation and mediator secretion in MCs and basophils.^{62,94} In addition, avapritinib can suppress IgE-dependent histamine release in basophils of patients with SM (P.V., unpublished observation, 2021). So far, whether midostaurin and/or avapritinib can also suppress MC activation triggered through other surface antigens, such as C5aR or MRGPRX2, remains unknown.

CLINICAL EFFICACY OF KIT TKIs IN PATIENTS WITH MC ACTIVATION: DO WE HAVE EVIDENCE FOR A NEW CONCEPT?

To date, little is known about the *in vivo* efficacy of KIT-specific or multitargeted TKIs in the treatment of patients with IgE-dependent allergies and MC activation disorders. This is of interest, as several studies have shown that KIT, the KIT ligand SCF, and MCs are involved in a number of atopic and/or allergic disease states^{23-26,95-98} and KIT-targeting drugs have been reported to interfere with, or even fully block, MC activation and mediator-induced symptoms in allergy-related animal models.⁹⁹⁻¹⁰²

However, very few studies have investigated the potential beneficial effects of KIT-targeting drugs in patients with severe allergic disorders in which MC activation apparently plays a role.

In 1 study, masitinib (3-6 mg/kg per day orally) was administered to 44 patients with severe corticosteroid-dependent asthma.¹⁰³ After 16 weeks, oral corticosteroid therapy could be reduced to a greater degree and in more patients in the treatment arm than in the placebo group.¹⁰³ However, lung function parameters did not change when the treatment group was compared with the placebo arm. Reported side effects during masitinib treatment were nausea (30.3%), a skin rash (30.3%), peripheral edema (18.2%), diarrhea (18.2%), vomiting (12.1%), fatigue (12.1%), and pruritus (12.1%).¹⁰³ No reports on patients treated with masitinib over 24 months (or longer) have been published so far.

In another study, 62 patients with poorly controlled or uncontrolled severe asthma who had airway hyperresponsiveness despite receiving maximal medical therapy were treated with

imatinib (400 mg per day orally) for 24 weeks.¹⁰⁴ Therapy with imatinib was found to reduce airway hyperresponsiveness more effectively in these patients than in the placebo control.¹⁰⁴ The MC numbers measured in the airway fluids declined in both groups without a significant difference between imatinib and the placebo control. Clinically relevant side effects included muscle cramps and hypophosphatemia, both of which were recorded more frequently in the imatinib arm.¹⁰⁴ Interestingly, the authors also reported on a slight decrease in serum tryptase levels and tryptase levels in the bronchial alveolar fluids.¹⁰⁴ However, no studies of long-term imatinib-treated patients with severe asthma have been published to date.

On the other hand, there are available studies in which changes in allergy-related symptoms in patients with advanced SM under long-term treatment with midostaurin have been reported.^{39,40} In most of these patients, relevant mediator-related symptoms decreased and did not return during long-term therapy. As already mentioned however, midostaurin also exerts direct effects on MC activation, which makes it difficult to define MC-depleting effects of this drug in the context of allergic reactions and related symptoms. In patients treated with avapritinib, symptoms also disappeared rapidly, and in many of these cases, MC depletion may indeed have been responsible (as an underlying drug action) for the observed improvement of their symptoms and their quality of life.^{43,44}

To date however, long-term results are lacking. Such data might not only support a new pharmacologic concept (MC eradication to stop allergies and MC activation disorders) but also provide additional proof that MCs are indeed the most important and relevant effector cells in human allergic disorders, thereby also reconfirming that the terms *MC activation disorders* (MCAD) and *MCAS* are justified.

There are, of course, additional remaining questions to consider. First, long-term treatment (over many years) with multitargeted anticancer agents, such as midostaurin or avapritinib, may cause unexpected long-term side effects. Therefore, 1 question is whether next-generation TKIs targeting KIT even more specifically or KIT-targeting antibodies, will be developed and may be even more suitable to apply in patients with MC-dependent (otherwise drug-resistant) allergic disorders or MC activation disorders. It is also worth noting that several different normal cell types, such as germ cells, hematopoietic stem cells, and melanoblasts, display KIT and that application of such drugs may be associated with, for example, mutagenic or teratogenic effects.

Another unresolved question is whether all atopic and allergic disorders are strictly MC-dependent. In fact, some of these disorders may also be triggered by basophils, which also express IgE receptors and contain mediators of allergic reactions. It is worth noting that neither midostaurin nor avapritinib (nor any other KIT-targeting TKIs) are known to eradicate blood basophils, although some of these TKIs do appear to decrease IgE- and antigen-dependent basophil activation.^{59,62,94} This is particularly relevant, as basophils may also participate in anaphylaxis reactions.^{24,105}

Finally, MCs are thought to have important functions, as for example, within the immune system (including contributing to resistance against certain parasite infections and mediating acute resistance to some venoms) and the reproductive system, and long-term depletion of MCs may not always be beneficial.^{2-4,9,106} In summary, more research and more clinical studies are required

to define the exact value of TKI-induced MC depletion therapies as a new pharmacologic concept and to translate such concepts into clinical practice in patients with MC activation disorders.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

MC activation occurs in a number of different disease states and pathologies. The resulting clinical symptoms represent an emerging challenge in daily practice. In severe forms, life-threatening anaphylaxis may occur and may lead to the diagnosis of MCAS. Recent data suggest that therapy with KIT-targeting drugs may lead to partial or even complete eradication of the MC lineage in patients with various MC diseases. In addition, some of these TKIs can also suppress IgE-dependent activation of MCs and basophils. Whereas several different KIT-targeting drugs that may suppress growth and activation of normal MCs are available, suppression or even eradication of neoplastic MCs exhibiting *KIT* D816V can be achieved only with novel TKIs directed against this KIT mutant form. The most effective and specific KIT D816V-targeting drug available to date appears to be avapritinib. In contrast, whereas midostaurin is less effective in blocking the activity of KIT D816V, this drug also blocks SYK activity and thus IgE-dependent MC activation. Both drugs suppress MC expansion in patients with *KIT* D816V-positive SM. Whether MC eradication induced by continuous treatment with an effective KIT TKI is safe and effective in patients with IgE-dependent allergies and whether it can help to avoid or mitigate the clinical symptoms of MC activation and anaphylaxis in these patients remain to be determined in forthcoming clinical studies.

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