REVIEW

Tyrosine Kinase Inhibitors for the Treatment of Mast Cell Diseases: Review and Update

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Abstract

Mast cell diseases (MCDs) comprise several entities that are characterized by activation and/or proliferation of mast cells (MCs), leading to the appearance of cardinal symptoms. Such activation may be due to exaggerated functioning of MCs or to a mutation in a tyrosine kinase (usually the D816V mutation in *KIT*), which is a characteristic feature of systemic mastocytosis (SM) and/or clonal MC activation syndromes. Depending on the MC burden and tissue infiltration, SM can be classified as advanced or nonadvanced. Traditionally, the treatment of MCDs has been based on best supportive care. In cases of advanced SM that responds poorly to best supportive care, management can also take the form of non–target-directed cytoreductive treatment, administration of monoclonal antibodies, targeted therapies, and even bone marrow transplantation. The advance of personalized medicine has led to the emergence of new and more specific tyrosine kinase inhibitors (TKIs), which achieve greater symptom control and improve disease course, sometimes leading to remission. In recent years, clinical trials have been carried out to evaluate the effectiveness of some of these TKIs in nonadvanced forms of mastocytosis, with eventual approval for this subtype in some cases. TKIs represent a major advance in the management of MCDs, with more patients being able to benefit from a treatment that addresses pathophysiology. We review the main TKIs currently available for SM, their indications, and their safety and effectiveness.

Key words: Avapritinib. Bezuclastinib. Elenestinib. Imatinib. Masitinib. Mast cell. Mastocytosis. Midostaurin.

Resumen

Las enfermedades mastocitarias (EMC) son un grupo de diferentes enfermedades que tienen en común una activación y/o acumulación del mastocito (MC), lo que conlleva la aparición de sintomatología cardinal correspondiente. Dicha activación puede deberse a un funcionamiento exagerado del MC o a una mutación en una tirosin quinasa (habitualmente la D816V de KIT), que es un rasgo característico de las mastocitosis sistémicas (MS) y/o los síndromes de activación mastocitaria clonal. En función de la carga mastocitaira y de la infiltración tisular, las MS se clasifican en diferentes tipos, que puede dividirse como avanzadas o no avanzadas. Tradicionalmente, el tratamiento de las EMC se ha basado en control sintomático. En los casos de MS avanzadas con mala respuesta a tratamiento sintomático, se pude utilizar también tratamiento citoreductor no selectivo, administración de anticuerpos monoclonales, terapias dirigidas o, incluso, trasplante de médula ósea. Con el avance de la medicina personalizada han ido apareciendo nuevos y más específicos inhibidores de tirosin quinasa (ITK) que están consiguiendo un mayor control sintomático e incluso una mejor evolución de la enfermedad, pudiendo llegar en ocasiones a la remisión. En los últimos años, además, se han realizado ensayos clínicos para valorar la efectividad de alguno de estos ITK en formas no avanzadas de mastocitosis, aprobando finalmente su uso para este subtipo de mastocitosis. Esto supone un gran avance en el manejo de este tipo de patología, pudiendo beneficiarse más pacientes de una herramienta terapéutica que controla la base fisiopatológica de su enfermedad. El trabajo actual, repasa los principales ITK existentes actualmente para las MS, sus indicaciones, así como su seguridad y efectividad.

Palabras clave: Avapritinib. Bezuclastinib. Elenestinib. Imatinib. Masitinib. Mastocito. Mastocitosis. Midostaurin.

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Introduction

Targeted therapy is widely used in personalized medicine. It enables diseases for which no specific treatment has yet been designed to be managed by targeting specific pathways involved in their physiopathology [1]. Tyrosine kinase inhibitors (TKIs) are a novel option in the treatment of cancer and chronic conditions such as chronic clonal myeloproliferative diseases [2].

Protein kinases phosphorylate tyrosine amino acid residues modifying other proteins by adding phosphates from adenosine triphosphate (ATP), which is necessary for signal transduction. Extracellular tyrosine kinases are known as receptor tyrosine kinases (RTKs) [1,2]. As RTKs are involved in many crucial cellular processes, mutations or changes in their functions may affect processes such as cell growth, survival, differentiation, migration, and metabolic regulation [3]. TKIs have revolutionized cellular target therapy. To transduce signals, RTKs are defined by an extracellular (EC) domain for ligand binding comprising a transmembrane single loop linked to a cytoplasmic region with tyrosine kinase activity (KD) arranged in a proximal lobe (-N) and a flexible distal lobe or carboxy-terminal domain (C-) (Figure 1). Adjacent juxtamembrane regions address autoregulation functions [3-5]. In their inactive form, RTKs are found as monomers autoregulated by juxtamembranes and arise from the interaction and binding of the EC domain with ligands that activate them through the dimerization process. The immunological processes that occur during their activation are detailed in Figure 2. The conformation of the EC domain helps to classify the more than 50 known RTKs into 20 families (Figure 3).

TKIs can be divided into monoclonal antibodies (mAbs) with RTKI function and small molecules (selective and multikinase small molecule inhibitors) [1]. While both mAbs and small molecules have the capacity to inhibit RTKs, the small molecules act by selectively blocking the tyrosine kinase intracellular domain, thus impeding phosphorylation of ATP, and their size enables them to access the intracranial space. Another advantage with respect to mAbs is their oral bioavailability, which is superior to that of intravenous or subcutaneous administration of the mAbs [1,5]. Despite their favorable safety profile, TKIs are not exempt from adverse effects, especially for multikinase small molecules, which are subject to a wide range of adverse effects directly related to their ability to inhibit multiple signaling pathways. To date, almost 100 small molecule TKIs have been developed

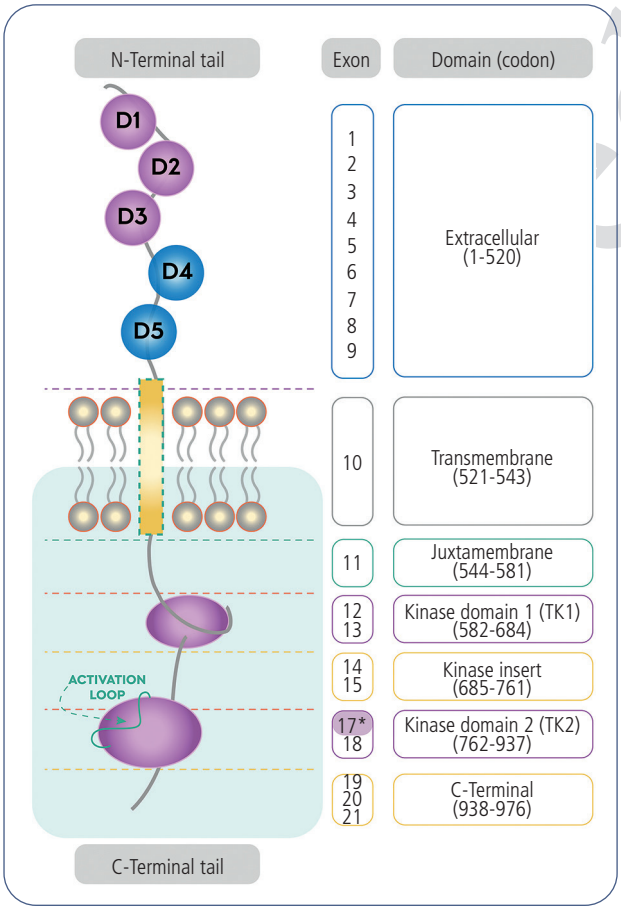

Figure 1. Structure of the KIT receptor.
*Exon 17: the most common *KIT* mutation Asp816Val (D816V) is localized here.

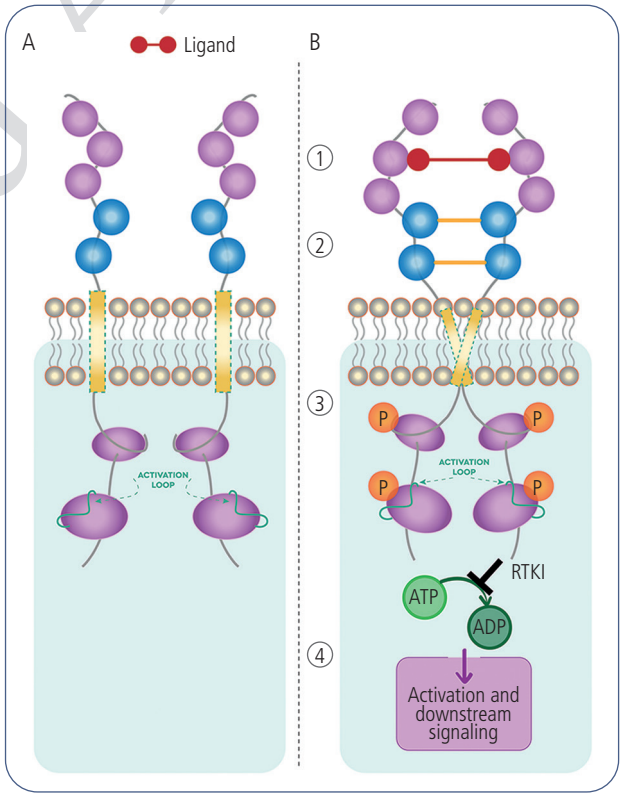

Figure 2. Immunological processes occurring during c-kit activation.
A, Inactive c-kit (monomer). B, Active c-kit (homodimerization). The following consecutive processes occur: 1, Binding of stem cell factor (SCF) to D1-D3 domains; 2, Conformational changes; 3, Autophosphorylation, which entails that ATP binds to the ATP binding region, the TK1 domain (N-lobe); and 4, Activation of downstream signaling by full activated c-kit.
⊢ Inhibits the action of.
ATP indicates adenosine triphosphate; ADP, adenosine diphosphate; RTKI, receptor tyrosine kinase inhibitor.

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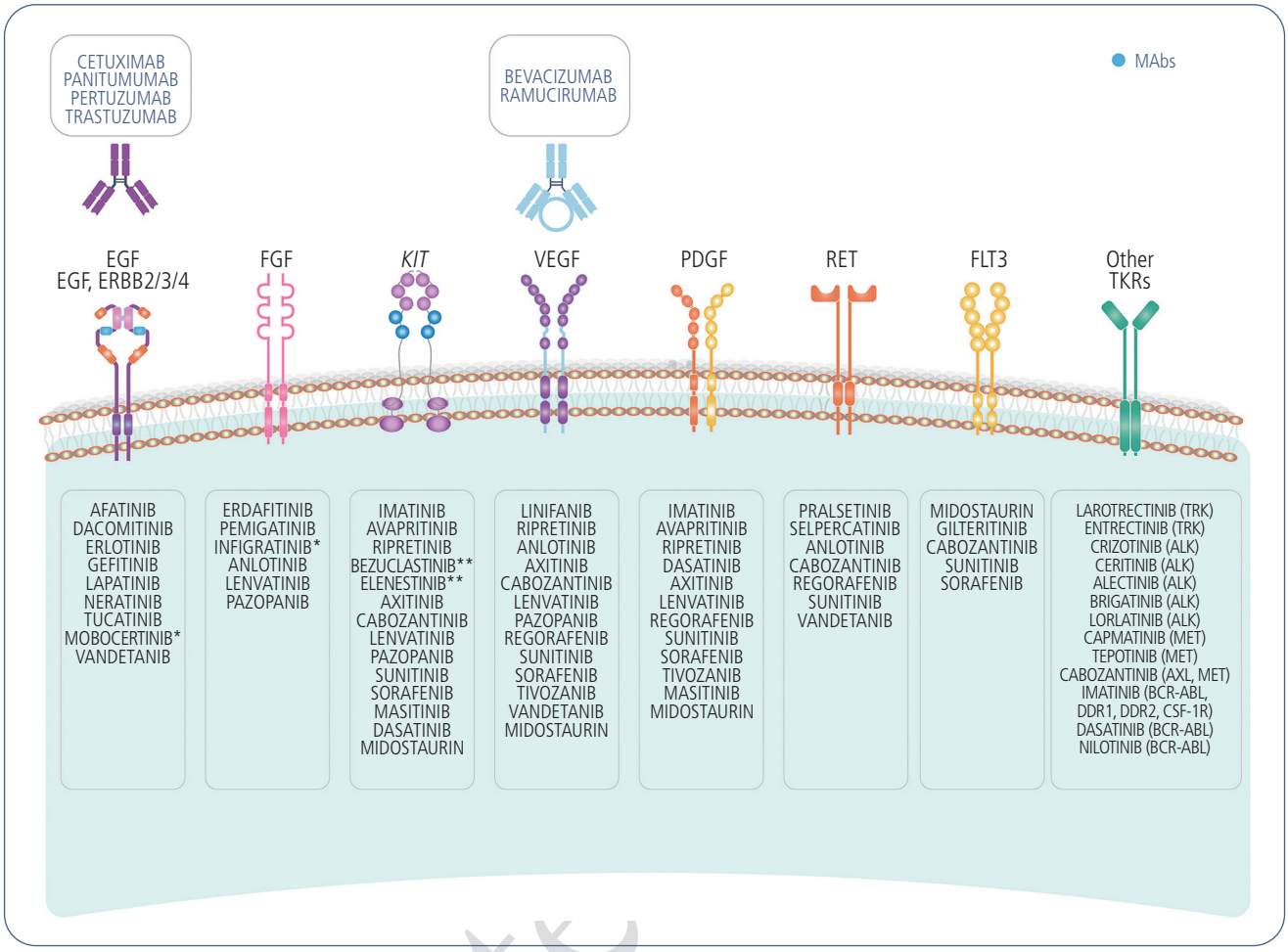

Figure 3. Main inhibitors of the tyrosine-kinase receptors according to their site of action.
*May not be available in all countries.
**Preclinical. Still in clinical trial phase.
ALK indicates anaplastic lymphoma kinase; Bcr-Abl (Tk), tyrosine kinase Bcr-Abl gene; CSFR-1R, colony-stimulating factor 1 receptor; DDR, discoidin domain receptor; EGF, epidermal growth factor; ErbB subfamily of tyrosine kinase receptors; FGR, fibroblast growth factor; FLT3, Fms-related tyrosine kinase 3 (fms, mononuclear phagocyte colony stimulating factor); *KIT*, proto-oncogene *KIT*; MAbs, monoclonal antibodies; MET, mesenchymal-epithelial transition factor; PDGFR, platelet-derived growth factor receptor; RET, rearranged during transfection; TKR, tyrosine kinase receptor; TRK, tropomyosin receptor kinase; VEGF, vascular endothelial growth factor.

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(Figure 3). *KIT*-targeting TKIs have been developed for advanced stages of mastocytosis, although their usefulness has recently been assessed in indolent systemic mastocytosis (ISM) [6,7]. The present article provides a review of recent treatments for systemic mastocytosis (SM), their indications, mechanisms of action, and adverse effects, as well as their current status. Our objective is to provide a guide for clinical decision making in the treatment of SM.

The Role of Protein Tyrosine Kinases in Mast Cell Disorders

Mast cell disorders (MCDs) comprise a heterogeneous group of diseases in which MCs are increased in number, more reactive than usual, or both. Under this definition, we can identify several entities. A patient is considered to have a mast cell activation syndrome (MCAS) if he/she fulfils the following criteria: (*1*) presence of acute symptoms characteristic of MC mediator release; (*2*) evidence of an increase in the release in at least 1 MC mediator (usually serum tryptase) during an acute episode; and (*3*) response to treatment with anti–MC mediator therapy, such as sodium cromoglycate, H1- and H2-antihistamines, leukotriene receptor antagonists, anti-IgE therapy, or a combination of these approaches [8,9]. In addition, MCAS is classified into primary MCAS (which includes monoclonal MCAS and mastocytosis) if MC clonality is proven and secondary or idiopathic MCAS. A new entity, hereditary α-tryptase (HαT), was recently described. HαT is a genetic trait that is closely related to MCD, affects about 5% of the population [10], and results in a higher number of copies of the gene coding for α-tryptase (*TPSAB1*). As a result, these patients may have baseline serum tryptase (bST) levels above 8 µg/L, although cases with bST levels below this cut-

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off point have also been described [10,11]. HαT is considered a risk factor for anaphylaxis [12], and unlike patients with MCAS, those carrying *TPSAB1* do not present with the usual cardinal release symptoms (Table 1).

MC clonality is determined by 2 biological parameters related to the pathogenesis of the disease itself: the presence of mutations in the proto-oncogene *KIT* or the expression of an MC with an aberrant phenotype (CD25, CD2, and/or CD30) in bone marrow or other tissue detected by flow cytometry [13]. This clonality is demonstrated using a highly sensitive method to assess an allele burden ≤0.1% of the D816V *KIT* mutation (eg, allele-specific quantitative PCR or digital droplet PCR) [14], while mutations involving other exons could be investigated by direct sequencing of purified bone marrow MC DNA [15]. Mutation detection assays based on sequencing, such as next-generation sequencing panels, lack the sensitivity to detect low-burden mutations, which are frequently associated with nonadvanced forms of SM [14]. The stem cell factor *KIT*, or CD117, is one of the most important receptors for the maturation, proliferation, survival, and differentiation of MCs and is persistently expressed independently of their cellular maturation stage, in contrast with other hematopoietic cells [16]. The CD117 ligand, stem cell factor, is a dimer able to bind 2 consecutive RTK monomers and activate them, leading to the triggering of signaling pathways such as JAK/STAT. Mutations in *KIT* lead to permanent activation of the *KIT* receptor independently of its binding to stem cell factor, resulting in deregulation of MC growth, differentiation, and activation. This leads to the presence of a broad range of possibly MC-related symptoms [17], as well as to accumulation in the skin and/or various organs and tissues, including, primarily, the liver, lymph nodes, spleen, bone marrow, and gastrointestinal tract [8]. The most common mutation is *KIT* Asp816Val (D816V), which is caused by a change of the amino acid aspartate to valine at position 816, although other atypical mutations affecting other codons can occasionally be observed [11,18]. This gene encodes a transmembrane TK, stem cell growth factor receptor [19]. Although most mutations are somatic, some cases of germline mutations related to the familial clustering of the disease have been described [8]. Genetic counseling is recommended in these cases [20,21].

Currently, the World Health Organization (WHO) classifies mastocytosis into (*1*) cutaneous mastocytosis (CM), (*2*) SM, and (*3*) mast cell sarcoma [22]. SM is further classified into bone marrow mastocytosis (BMM), ISM, smoldering SM (SSM), aggressive SM (ASM), SM with an associated hematological neoplasm (SM-AHN), and MC leukemia (MCL). According to presently accepted nomenclature, ASM, SM-AHN, and MCL are considered advanced types of SM (AdvSM) [8,22]. Well-differentiated (WD) morphology [23] is a rare pattern characterized by round and well-granulated MCs, CD30 expression in the absence of aberrant CD25/CD2 phenotypic expression, and, frequently, child onset and familiar aggregation [24]. WDSM may be found in any variant of SM [25].

The clinical presentation of SM varies considerably, even in patients with the same type of SM, and although the frequency of anaphylaxis inversely correlates with MC burden and is higher in nonadvanced types of SM [26], baseline symptoms and tissue infiltration by MCs tend to become more frequent and severe as the disease progresses. The treatment of MCD involves individualized and multidisciplinary management, with the main objective being to reduce the frequency and intensity of symptoms [26-28]. All patients must be educated about the potential triggers of MC degranulation, recognition of symptoms, risk of anaphylaxis, and the need for emergency treatment in the event of an acute episode, including self-injectable epinephrine if necessary. Best supportive care (BSC) antimediator treatments include H1- and H2-antihistamines,

Table 1. Main Mast Cell Pathologies Classified According to Molecular Biology Criteria.

Genetics		Cause of MCA	Entity	Diagnostic feature
KIT	Clonal MCAS (KIT-mutated MC)	Primary MCD	SM	World Health Organization major criterion and ≥1 minor criteria or ≥3 minor criteria (without the major criterion) are fulfilled.
			MMAS	MCAS and clonality criteria are met ($CD25^+/CD2^+/CD30^+$ and/or *KIT* D816V mutation is detected in MCs).
	Nonclonal MCAS (wild type KIT MC)	Secondary	Allergy Other underlying entities (eg, cancer, autoimmune disorders, inflammatory diseases).	MCs are activated because of underlying conditions without clonal MCs.
		Idiopathic	Idiopathic anaphylaxis Idiopathic MCAS	MCA is detected, but neither primary nor secondary causes are detected.
TPSA1B increased number (with clonal or nonclonal MCs)		Germline increased number of copies in the TPSAB1 gene encoding for α-tryptase	Hereditary α-tryptasemia	Baseline serum tryptase ≥ 8 μg/L[a] Detection of increased TPSAB1 copy number copies

Abbreviations: MC, mast cell; MCA, mast cell activation; MCAS, mast cell activation syndrome; MCD, mast cell disorder; SM, systemic mastocytosis; MMAS, monoclonal mast activation syndrome.

[a]Chosen as a reference level, although there may be cases with lower values.

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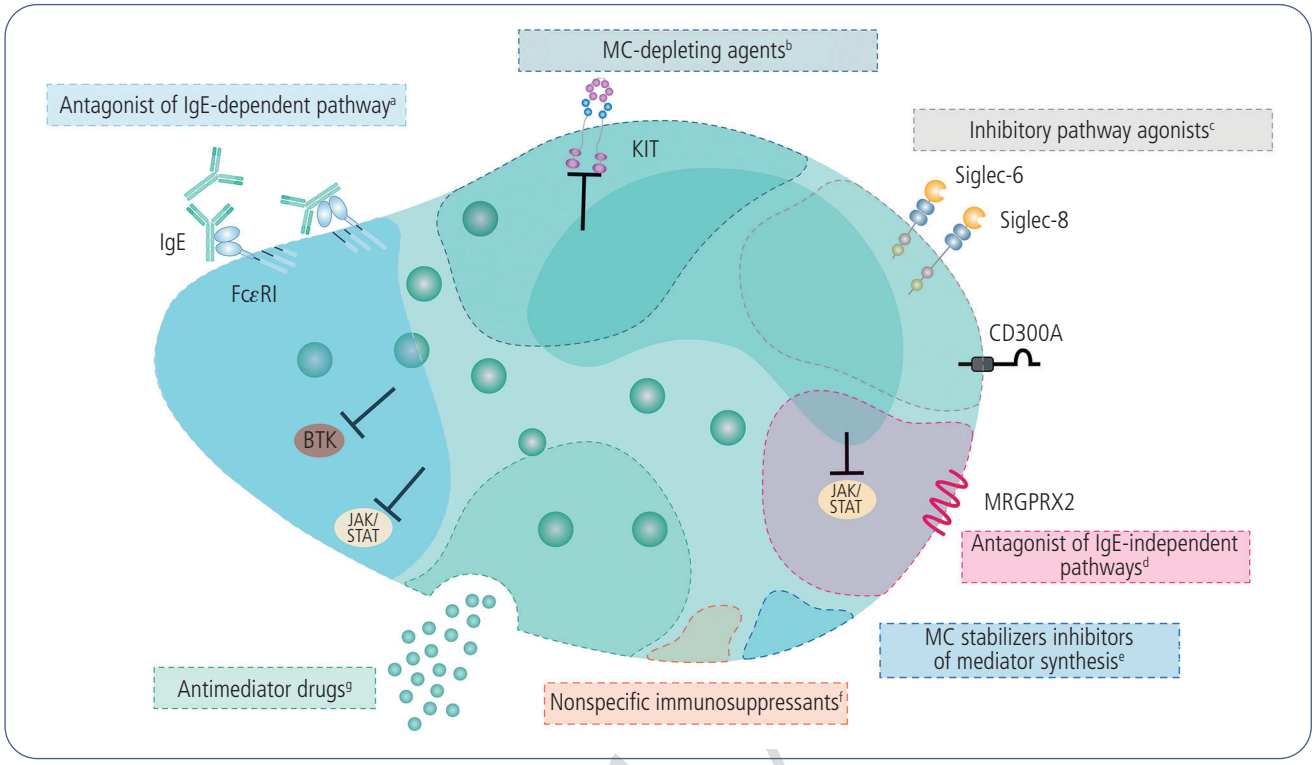

Figure 4. Therapeutic targets of the mast cell. Adapted from [29].
[a]Including anti-IgE treatments, BTK and JAK/STAT inhibitors such as designed ankyrin repeat proteins (preclinical), Fc-fusion proteins, and single-domain antibodies.
[b]Including the tyrosine-kinase receptor inhibitors depicted in figure 2.
[c]Including inhibition of CD300A and preclinical antibodies against siglec-6 and -8
[d]Including MRGPRX2 receptor.
[e]Including sodium cromolyn and acetylsalicylic acid.
[f]Including corticosteroids, cyclosporin, hydroxychloroquine.
[g]Including H1-and H2-antihistamines.
⊣ Inhibits the action of.
BTK indicates Bruton tyrosine kinase; CD300A, cluster of differentiation 300A gene; FceRI, high affinity immunoglobulin E receptor; IgE, immunoglobulin E; JAK/STAT, Janus kinases (JAKs), signal transducer and activator of transcription proteins (STATs); *KIT*, proto-oncogene *KIT*; MC, mast cell; MRGPRX2, Mas-related G-protein coupled receptor member X2; Siglec-6, sialic acid-binding Ig-like lectin 6; Siglec-8, sialic acid-binding Ig-like lectin 8.

leukotriene inhibitors, disodium cromoglycate, and even oral corticosteroids or omalizumab (anti-IgE therapy) (Figure 4). In cases of IgE-mediated allergy, the administration of specific immunotherapy, such as Hymenoptera venom, is also effective [30]. In recent years, the emergence of TKIs has revolutionized the treatment of patients with MCD [4,31]: firstly, in contrast to previous treatments, by avoiding the use of non–target-directed cytoreductive drugs in patients with advanced forms of the disease, who usually have more frequent and more intense symptoms, as well as more complications [32-37]; and secondly, by improving the quality of life of patients with nonadvanced forms of the disease that remain poorly controlled despite high-dose treatment with antimediators.

Main TKIs Used in Mast Cell Diseases

Imatinib

Imatinib was developed as the first oral signal transduction inhibitor to specifically target several protein TKs, such as wild-type *KIT*, BCR-ABL, FLT3, PDGFRα, PDGFRß, and CSFR1. It also demonstrated in vitro efficacy against certain transmembrane (F522C or K509I) and juxtamembrane (V560G) *KIT* mutations, outside the activation loop of *KIT*, but not the common kinase (D816V) domain mutations or juxtamembrane (V559I) *KIT* mutations (Table 2) [38]. The technical data provided by the manufacturer [39] describe its utility in patients who present the FIP1L1-PDGFRα fusion kinase or a *KIT* mutation in the juxtamembrane region (eg, F522C or K509I).

Imatinib has remarkable clinical activity in patients with chronic myeloid leukemia and malignant gastrointestinal stroma tumors [40]. Furthermore, it is currently approved by the United States Food and Drug Administration (FDA) for adult patients with ASM without the *KIT* D816V mutation or with unknown *KIT* mutational status. This approval was based on the positive effect of the drug on patients with chronic eosinophilic leukemia or myeloproliferative variant hypereosinophilic syndrome characterized by PDGFRα rearrangements. Imatinib is not approved for nonadvanced mastocytosis or for most patients with SM, who carry the

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D816V *KIT* mutation. Patients carrying the mutation show intrinsic resistance to imatinib due to a conformational change in the enzymatic pocket that blocks the binding of the drug to the receptor [41].

Results on the use of imatinib in SM have been reported for 5 affected patients recruited in an open-label, multicenter, phase 2 study [42] and in 2 case series covering 26 additional patients [43,44]. A complete response was defined as the

Table 2. Profile of Tyrosine Kinase Inhibitors Used in Mast Cell Diseases.

Drug	Mechanism of action	Clinical usage and current development stage		Overall effectiveness	Adverse effects[a]
Imatinib	- Inhibition of WT-*KIT* (but not D816V-mutated *KIT*). - Outside exon 17: inhibition of *KIT* K509I, F522C, and V560G mutations.	- AdvSM without KIT D816V mutation or unknown mutation status. - Age: ≥18 y[b] - Dose: 400 mg/d[b]	FDA-approved and commercialized.[c]	Moderate response, restricted to WDSM with sensitive *KIT* mutation and ASM with *KIT* D816V-unmutated.	Peripheral edema, musculoskeletal pain, fatigue, diarrhea, nausea, vomiting, abdominal pain, skin rashes.
Masitinib	Inhibition of WT-*KIT* (but not D816V-mutated *KIT*).	- AdvSM without the usual mutation 816 or with wild-type KIT. - Age and dose: NA.	Approved and commercialized only for animal use.[d]	Effective in reducing MC activation with modest efficacy in the control of pruritus, flushing, depression, and fatigue.	Asthenia, nausea, vomiting, eye or peripheral edema, muscle spasms, rash and itching.[e]
Midostaurin	Inhibition of WT-*KIT* and mutated *KIT* (all common mutated forms, including D816V).	- AdvSM. - Age: ≥18 y. - Dose: 300 mg/d.	FDA- and EMA-approved and commercialized.	Decrease MC burden and sBT. Improve patient reported symptoms and QoL.	Nausea, vomiting, diarrhea and fatigue.
Avapritinib	Highly selective and potent inhibitor of D816V-mutated *KIT*.	- AdvSM and ISM. - Age: ≥18 y. - Dose: maximum of 200 mg/d in Adv-SM and of 25 mg/d in ISM	FDA- and EMA-approved and commercialized.	- In AdvSM: enhanced survival, reductions in measures of MC burden, and normalization of organ damage. - In ISM: decrease in TSS, decrease in skin lesions, and decrease in MC burden and improvement of QoL.	Periorbital and peripheral edema, neutropenia and trombopenia. Dose dependent.
Bezuclastinib[f]	Highly selective *KIT* inhibitor against mutations in exon 17, including D816V.	- AdvSM, SSM, and ISM. - Age: ≥18 y. - Dose: 200 mg/d in AdvSM, and 100 mg/d in non-AdvSM.	Phase 3 for AdvSM. Phase 2 for non-AdvSM (ISM and SSM).	- In AdvSM: reductions in measures of MC burden. - In non-AdvSM (SSM and ISM): improvement in symptom severity and health-related quality of life.	Preliminary data: changes in hair color, taste alterations and peripheral or orbital edema.
Elenestinib[f]	Highly selective and potent inhibitor of D816V-mutated *KIT*.	- AdvSM, SSM and ISM. - Age: ≥18 y. - Dose: 50 mg vs 75 mg vs 100 mg/d.[f]	Phase 2/3 for ISM. Phase 1/2 for AdvSM.	Decrease in clinical symptoms and MC burden.	Data are scarce. Preliminary data show no treatment-related serious adverse events.

Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; EMA, European Medicines Agency; FDA, United States Food and Drug Administration; ISM, indolent systemic mastocytosis; *KIT*, proto-oncogene *KIT*; MC, mast cell; MCD, mast cell disease; NA, not applicable; QoL, quality of life; sBT: serum baseline tryptase; SSM, smoldering systemic mastocytosis; TSS, total symptoms score; WDSM, well-differentiated systemic mastocytosis; WT, wild type.

[a]Periodic analytical determinations should be performed to assess cytopenia.

[b]There are case series reported with children successfully treated with imatinib, at a dose of 100 mg/d.

[c]Authorized by the FDA and EMA for other hematological pathologies.

[d]Used in humans since 2016, its marketing authorization was refused by the FDA and EMA in 2018. At present, is only commercially available for use in animals.

[e]Absence of cardiotoxicity and less hematological toxicity than imatinib.

[f]Clinical trial in process. Currently under study.

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combination of absence of symptoms, <5% MCs in bone marrow aspirate, absence of focal infiltrates of MCs, complete disappearance of skin lesions, normalization of bST levels and urinary N-methylhistamine excretion, and no concurrent therapy. Complete response was attained in 1 patient, who expressed the FIP1L1-PDGFRα rearrangement gene [44], and in 3 patients who developed eosinophilia in the absence of the D816V *KIT* mutation [43]. Major responses were defined as a reduction >50% in bST levels, urinary N-methylhistamine excretion, or skin lesions, <10% MCs in bone marrow aspirate, and the absence of progression of SM at other sites. Major response was achieved in 5 patients (4/5 had the D816V+ *KIT* mutation) [44]. Partial response, with a reduction in bST, was reported in another case with the D816T *KIT* mutation [42]. The hematological response was found to be complete in 7/20 patients with the FIP1L1-PDGFRα fusion kinase and partial in 2/20 patients who presented a *KIT* mutation in the juxtamembrane region (F522C and K509I, respectively). Among 4/20 patients who had a D816V *KIT* mutation, a response was recorded in only 1 patient, who also had chronic myeloid leukemia. Interestingly, 7/15 cases presented a partial hematological response in the unknown or no-cytogenetic-abnormality-detected group. In addition, the response to imatinib was reported in a phase 4 clinical trial in 10 adult patients who presented with mastocytosis lacking exon 17 *KIT* mutations [15]. Sequencing of other *KIT* exons only revealed a germline K509I mutation (exon 9) in the 3 familial WDSM patients included. Among the 10 cases, only 1 patient, who had SM-AHN, did not fulfill the criteria for WDSM. This study reported an overall response rate of 50%, including early and sustained complete response (defined as complete resolution of all disease signs and symptoms including bone marrow MC infiltration, skin lesions, organomegaly, and MC mediator release–associated symptoms, plus a decrease in sBT < 11.5 μg/L) in 4 patients, 3 of whom had extracellular *KIT* mutations. In addition, partial response (defined as ≥50% reduction in bone marrow MC infiltration and improvement in skin lesions and/or organomegalies) was detected in 1 case.

In pediatric mastocytosis, 4 highly symptomatic children with CM were successfully treated with imatinib. One had a somatic deletion of codon 419 in exon 8 (c.1255_1257delGAC)—this was sensitive to imatinib—together with a novel germ line p.Ser840Asn substitution encoded by exon 18 in the c-kit kinase domain [45]. The other 3 had diffuse CM: 1 presented an M541L polymorphism in the transmembrane domain of *KIT* (sensitive to imatinib) [46], whereas the other 2 had a *KIT* mutation in exon 8 (p.Asp419del) [47]. All these data support the hypothesis that response to imatinib in SM patients depends on the presence of imatinib-sensitive mutations either involving *KIT* (eg, juxtamembrane or transmembrane *KIT* mutations) or PDGFR (eg, FIP1L1-PDGFRα rearrangement) rather than on the absence of the D816V *KIT* mutation [48].

Therapy with imatinib is generally well tolerated. As reported by the manufacturer, cytogenetic abnormalities might be observed in 70% of ASM patients [39]. The most common nonhematological adverse events include mild-to-moderate peripheral edema (up to 60%), musculoskeletal pain (47%), fatigue (39%), diarrhea (46%), nausea (71%), vomiting (54%), and abdominal pain and skin rashes (36%) [47].

Masitinib

Masitinib is a multitarget protein kinase inhibitor able to reversibly bind both free c-kit and c-kit/ATP substrate complex in some mutated c-kit forms and on exon 11 mutations, ie, V560G, but not on the most frequent one (about 85%-90%), namely, D816V on exon 17. It is also active on the proteins PDGRFα and FIP1L1-PDGRFα, has moderate action on cFms and LynB, and is inactive on major receptors such as Bcr-Abl, Flt3, VEGFR1, VEGFR2, and EGFR [49,50]. The inhibitory action of masitinib on Lyn/Fyn also plays a significant role in controlling MC degranulation, independently of the c-kit signaling pathway and survival of MCs. It has an aminothiazole group that is more hydrophobic than the pyrimidine ring of imatinib and enables the molecule to interact with c-kit through a longer-lasting link than imatinib. Masitinib is less effective or even noneffective against *KIT* D816V and, thus, recommended only in patients with other *KIT* mutant forms (noncodon 816 mutations) or with wild-type *KIT* [7,51].

As systemic mastocytosis is a rare disease, there are no standardized response criteria for evaluating trends in pharmacologic treatments [49]. One large-randomized phase 3 study [52] with masitinib in 135 patients with symptomatic ISM concluded that it reduced MC activation with modest efficacy in the control of pruritus, flushing, depression, and fatigue, with an overall cumulative response rate of 18.7% vs 7.4% in the placebo arm. In a phase 2 multicenter study evaluating masitinib in 25 patients with SM and comorbidities (eg, flushes, depression, pruritus) and poor quality of life [53], all clinical symptoms improved between week 4 and week 12. A clinical response was observed in 14/25 patients. This early response was also observed in 1 patient with MCL after 3 months of treatment and was characterized by improvement in symptoms and the disappearance of circulating MCs (from 7% to 0%) and c-kit–expressing cells (from 46% to 2%) [54]. As reported, depression is a frequent symptom in patients with SM. Masitinib induced a significant improvement in depression (67% of cases), with recovery in 75% of cases in a study involving 288 patients [55].

Masitinib is less toxic than imatinib because it is more selective towards TK targets. The frequency of adverse effects (AEs) during the first 12 weeks is relatively high (84%-95%), although most AEs were mild or moderate and generally resolved spontaneously or with symptomatic treatments. The most frequent AEs were asthenia (83%), nausea/vomiting (44%-72%), eye or peripheral edema (44%-67%), muscle spasms (28%-40%), rash (28%-40%), and itching (33%) [52,56]. Compared with other TKIs (mainly imatinib), masitinib is not associated with cardiotoxicity and only scarcely associated with less frequent hematological reactions [49]. AEs could be mitigated via implementation of a dose-escalation scheme. The oral bioavailability of masitinib is not linear, and the risk of increased systemic exposure can be reduced with 2 equal doses twice daily rather than a higher dose administered once daily [49].

Masitinib is currently only commercially available for use in animals. Although it was first used in humans in 2016 and administered as an orphan medication in amyotrophic lateral sclerosis (ALS), its marketing authorization for SM and ALS

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was refused by the FDA and European Medicines Agency (EMA) in 2018 and recently again in 2024 [57]. Nevertheless, many clinical trials have been/are being performed with masitinib for treatment of multiple tumors, various diseases (respiratory, neurological, inflammatory), and even acute ischemic stroke [49]. One clinical trial (NCT05449444) on treatment of severe MCAS is currently recruiting.

Midostaurin

Midostaurin (PKC412) is a potent multikinase inhibitor that targets several TKRs, such as KIT, FLT3, PDGFR, VEGFR-2, and PKC. Binding to the catalytic domain of kinases, it inhibits mitogenic signal transduction triggered by several cell growth factors, thus stopping the cell cycle and inducing apoptosis [58]. In vitro studies have shown that midostaurin is active on all common mutated forms of c-kit, including D816V. It inhibits c-kit phosphorylation induced by stem cell factor and, in turn, impairs MC proliferation and survival [58-60]. It was approved by the FDA and the EMA in 2017 for monotherapy in adult patients with advanced forms of SM.

The efficacy of midostaurin in AdvSM has been evaluated in 2 clinical trials. A multicenter phase 2 study (CPKC412D2213) evaluated 26 patients with ASM or MCL and at least 1 sign of organ damage [61]. The reported overall response rate (ORR) according to the proposed criteria [62,63] was 69%, with 38% of major responses during the first 12 cycles [61]. After a median 10-year follow-up, complete remission was achieved in 2 patients, and a reduction ≥50% in MC burden and bST levels was observed in 68% and 46% of patients, respectively. The median overall survival was 40 months (range, 1.2-134.6); survival was 18.5 months for MCL patients. Furthermore, the multicenter, international, single-arm, open phase 2 study CPKC412D2201 evaluated 89 adult patients with AvdSM and at least 1 measurable clinical finding. The authors reported that 87% of patients were positive for the *KIT* D816V mutation [64]. The ORR, according to the response criteria [62,63,65,66], was 60% (95%CI, 49-70; *P*<.001). Major responses, defined as a complete resolution of damage to at least 1 organ, were found in 45% and partial responses in 15% [64,67]. Responses were detected within the first 3 months. The median duration of the response was 24.1 months. Response rates for the different AdvSM subtypes were 75% in ASM, 58% in SM-associated clonal hematological non-MC lineage disease, and 50% in MCL. Bone marrow MC burden and bST levels decreased by a median of 59% and 58%, respectively, and spleen volume decreased in 77% of patients with splenomegaly at baseline. The median OS was 28.7 months, with a median progression-free survival of 14.1 months. Of note, the median survival of patients with the D816V *KIT* mutation was longer than those with no or unknown mutation status (33.9 vs 10 months). In a post hoc analysis using more recent and strict response criteria [67], the ORR was lower (28%).

Midostaurin has also been associated with significant improvements in patient-reported symptom burden (Memorial Symptom Assessment Scale) and quality of life (SF-12) in both physical and mental health scores [68]. The improvement in symptoms could be related to the ability of midostaurin to inhibit the IgE-dependent release of histamine from MCs and basophils [69,70]. These results provided the rationale for exploring midostaurin in nonadvanced forms of mastocytosis, in which mediator-related symptoms are the main clinical manifestation. Thus, the drug was evaluated in an open label, nonrandomized, single-center, phase 2 trial (NCT01920204) in 20 adult patients with ISM and severe mediator-related symptoms not controlled with BSC [71]. After 12 weeks of treatment, the symptom score (Mastocytosis Symptom Assessment Form) improved in 75% of patients, with a significant median (IQR) reduction of 35% in symptom severity (16%-56%, *P*<.01). Quality of life, assessed using the mastocytosis quality-of-life questionnaire, improved by a median 29% (16%-47%, *P*<.001) after 24 weeks of treatment. bST levels decreased significantly after 4 weeks (from 36 to 15.5 μg/L, *P*<.001), as did the frequency of the cutaneous lesions of mastocytosis, with a median 40% reduction in the SCORing MAstocytosis Index in 80% of affected patients. Treatment discontinuation at week 24 was followed by a rapid relapse in most cases.

Midostaurin is metabolized extensively in the liver, mainly through CYP3A4 enzymes, with the possibility of interference with other drugs catabolized by the same route. The main reported AEs were nausea (85%) and vomiting (82%), which are generally well managed with antiemetics, as well as diarrhea (54%), peripheral edema (35%), and fatigue (28%) [61,64,71-73]. Grade 3 or 4 nonhematologic AEs included fatigue (9%), diarrhea (8%), sepsis (7.7%), pneumonitis (7%), and febrile neutropenia (7%). Grade 3 or 4 neutropenia, anemia, and thrombocytopenia were observed in 24%, 41%, and 29% of patients, respectively, mainly in those with cytopenia at baseline. Photosensitivity was observed in 25%. Other laboratory test abnormalities included increases in glucose, lipase, and transaminase levels. The dose can be reduced or interrupted in cases of hematological toxicity or other grade 3 or 4 toxicities, such as nausea, vomiting, or diarrhea. Midostaurin may be interrupted until the cell count or symptoms improve and then resumed at 50 mg bid, increasing gradually to 100 mg bid.

Avapritinib

Avapritinib (BLU-285) is a highly selective and potent inhibitor of D816V-mutated *KIT*. In AdvSM (NCT02561988 EXPLORER and NCT03580655 PATHFINDER studies), oral administration of 200 mg of avapritinib was associated with significantly enhanced survival, reductions in MC burden, and normalization of organ damage [74,75]. Early clinical evaluation of avapritinib in a phase 1 study revealed marked activity in patients with diseases associated with activation loop mutations in *KIT* (ASM and gastrointestinal stromal tumor) and *PDGFRα* (gastrointestinal stromal tumor) [76]. Moreover, an unanchored matching-adjusted indirect treatment comparison in AdvSM using the data from the avapritinib trials PATHFINDER and EXPLORER and the midostaurin trials D2201 and A2213 suggested that compared with midostaurin, avapritinib improves overall survival with a lower risk of death (HR, 0.44; 95%CI, 0.25-0.76) and adjusted ORs for the overall response rate [77]. Within the landscape of TKIs, avapritinib emerges as a distinct contender, demonstrating heightened selectivity for the inhibition of D816V-mutated *KIT* when compared with midostaurin [76].

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Furthermore, avapritinib is the first TKI to be approved for ISM. The PIONEER study (NCT03731260), a phase 2, multipart, randomized, placebo-controlled, double-blind trial investigating avapritinib plus BSC in patients with moderate-to-severe symptomatic ISM showed that avapritinib 25 mg was superior to placebo in reducing uncontrolled symptoms and MC burden in patients [78]. The patients enrolled had a baseline total symptom score (TSS) of ≥28 (out of 110) despite receiving BSC, indicating inadequately controlled symptoms. A total of 212 patients were randomly assigned in a 2:1 ratio to receive either avapritinib 25 mg once daily plus BSC (141 patients) or placebo plus BSC (71 patients) for 24 weeks. Compared to the placebo group, the TSS decreased significantly in avapritinib-treated patients, who achieved a 50% reduction in bST (P=.001) and experienced a 50% reduction in *KIT* D816V variant allele frequency (VAF) in peripheral blood (P=.001). In addition, by week 22, 24% of avapritinib patients had reduced or discontinued treatment with BSC compared with 13% in the placebo group. The overall incidence of AEs was similar between the groups, with low rates of discontinuation [78]. Moreover, avapritinib-treated patients experienced improvements from baseline to 24 weeks in all quality of life and health status measures [79]. The ongoing 5-year open-label extension will evaluate the long-term efficacy and safety of avapritinib.

Bezuclastinib

Bezuclastinib (CGT9486) is a potent oral and highly selective type 1 *KIT* inhibitor targeting exons 9, 11, 17, and 18, including the D816V mutation, without altering other closely related kinases [80].

For treatment of AdvSM, bezuclastinib was analyzed in a phase 2, randomized, open-label, clinical trial (APEX, NCT04996875) to evaluate safety and efficacy in 32 adult patients diagnosed with ASM, SM-AHN, and MCL and with at least 1 clinical finding, bST of ≥20 ng/mL, and baseline platelet count ≥50 × 10^9/L. The median bone marrow MC burden was 30% at baseline [80]. According to the preliminary data and proposed consensus response criteria in AdvSM [67], treatment with bezuclastinib resulted in 56%-75% overall survival with an early benefit (from week 8); bST decreased by >50% from baseline in 94% of patients, *KIT* D816V VAF decreased in 93%, and the bone marrow MC burden decreased by 97%. Optimal efficacy and safety outcomes were observed with the 100-mg twice daily dose (200 mg per day) [81]. At 12 weeks, bezuclastinib improved symptom severity (51% reduction according to the Mastocytosis Symptom Severity Daily Diary [MS2D2], achieved in 70% of patients) and health-related quality of life (49% improvement measured by the MC-QoL questionnaire) compared with placebo.

Bezuclastinib is also being studied in a phase 2 randomized, double-blind, placebo-controlled, clinical trial (SUMMIT, NCT05186753) in patients with non-AdvSM (ISM and SSM) with moderate-to-severe symptoms receiving ≥2 BSC medications. While promising preliminary results have been obtained, the study has yet to be completed [82]. In combination with sunitinib, bezuclastinib is also being assessed in an ongoing phase 3 study in advanced gastrointestinal stromal tumors. In the first part, safety was proved [83]. In the ongoing second part, progression-free survival will be the primary endpoint, in addition to additional efficacy and safety [84].

Bezuclastinib has limited ability to cross the blood-brain barrier, and no central nervous system toxicities, such as the intracranial bleeding caused by avapritinib, have been reported [85]. Regarding hematologic toxicity, AEs were less common than with other TKIs and included neutropenia (19%), thrombocytopenia (22%), and anemia (13%). The most common nonhematologic AEs were changes in hair color (34%), taste alterations (19%), and peripheral or orbital edema (13%).

Elenestinib

Elenestinib (BLU-263) is a novel orally bioavailable small molecule, next-generation TKI of *KIT* D816V that is currently under investigation [86,87]. Its selectivity and potency are comparable to those of avapritinib, although its potential for penetrating the brain is limited, thus potentially leading to intracranial bleeding and cognitive impairment.

The HARBOR trial (NCT04910685) is a multipart, randomized, double-blind, placebo-controlled, phase 2/3 study comparing the efficacy and safety of elenestinib (BLU-263) plus BSC with placebo plus BSC in patients with ISM whose symptoms are not adequately controlled by symptomatic treatment [88]. Preliminary results after 12 weeks of treatment have been reported for a total of 122 patients with ISM; 39 were blinded and randomized to elenestinib or placebo, and 83 were treated with open-label elenestinib in the pharmacokinetics groups at 50 mg, 75 mg, and 100 mg. After 12 weeks of therapy, elenestinib demonstrated beneficial effects on TSS and biomarkers of MC burden. Compared with placebo, sBT decreased in patients receiving elenestinib at 25 mg, 50 mg, and 100 mg (−15.4%, −50.9%, and −68.4% vs 3.3%, respectively), as did the VAF of *KIT* D816V (−37.5%, −70.3%, and −77.0% vs −2.5%, respectively). After a median treatment duration of 35.3 weeks, elenestinib was well-tolerated at all dose levels. There were no treatment-related serious AEs and no treatment-related AEs that led to discontinuation. The open-label extension is currently ongoing. This agent is also under investigation for patients with AdvSM, SM-AHN, and other hematologic malignancies in the AZURE study (NCT05609942) [89].

Conclusions

Precision medicine uses data on the genomic, environmental, and lifestyle characteristics of an individual to provide a more precise approach to the prevention, diagnosis, and treatment of MCD. Targeted therapies are a key part of this individualized management, which aims to provide patients with the best possible treatment. Tyrosine kinases are involved in many cellular functions, including cell signaling, cell growth, and cell division. TKIs can therefore specifically block the action of 1 or more kinases. TKIs should be chosen carefully, balancing efficacy and toxicity; as a rule, the higher specificity of the drug, the better its safety profile.

Mast cell diseases, mainly mastocytosis, can present with a wide range of symptoms, from mild skin symptoms to

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anaphylaxis (with or without a known etiology), that severely compromise and affect quality of life. In the absence of curative therapy, the usual management of SM has been symptomatic control with antimediator medication. In advanced SM, non–target-directed cytotoxic treatment was traditionally added as a means of controlling MC burden, always balancing the assumable benefits against the risk of adverse effects [32]. The initial introduction of TKIs such as imatinib and masitinib [40,49] as targeted cytoreductive therapy was an unprecedented advance over existing treatments (interferon γ, cladribine, hydroxyurea, allogeneic transplantation) with limited efficacy [32-37]. The subsequent arrival of new TKIs for patients with the most frequent *KIT* mutation (D816V), supported by the good results of trials with midostaurin [61-67], was another major advance. In addition to better symptom control, disease course improved and even remitted. Therapies for advanced types of SM have broadened their spectrum to nonadvanced forms, with avapritinib [76-78] already indicated for ISM and molecules such as bezuclastinib [81-83] and elenestinib [88] in the later phases of clinical trials. Information on the better safety profile of bezuclatsinib and elenestinib must be confirmed in real-life studies or larger phase 3 clinical trials. Additionally, such favorable results have opened the door to new clinical trials (NCT05449444) in other MC-related entities, such as MCAS.

Although our approach to patients with nonadvanced SM treated with TKIs should be cautious and the clinical course should be monitored, management of MCDs is more promising than it has been for many years. The availability of effective, more tolerable targeted therapies might significantly improve the management of SM and patient quality of life.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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CME Items

1. Which of the following is correct in relation to mast cells?
   a. For diagnosis of clonality, both the presence of a mutation in *KIT* and the expression of an aberrant phenotype (CD25, CD2, or CD30) must be determined.
   b. Once the cells are purified, it is not necessary to use highly sensitive in vitro methods for diagnosis of clonality.
   c. The most frequent mutation in nonclonal MCAS is the change from valine to asparagine.
   d. None of the above is correct.

2. Which of the following statements is false regarding the different types of systemic mastocytosis (SM) according to the current classification?
   a. The World Health Organization classifies mastocytosis into cutaneous mastocytosis, systemic mastocytosis, and mast cell sarcoma.
   b. There are different types of SM.
   c. Well-differentiated is considered a separate SM variant.
   d. According to the accepted nomenclature, aggressive mastocytosis, SM with an associated hematological neoplasm, and mast cell leukemia are considered advanced types of SM.

3. In which of the following can imatinib prove useful?
   a. Aggressive systemic mastocytosis. It is not necessary to investigate the mutational status of *KIT*.
   b. Advanced systemic mastocytosis associated with the PDGFRa rearrangement.
   c. Well-differentiated systemic mastocytosis with the *KIT* V560G mutation.
   d. Imatinib can be useful in b and c.

4. Regarding the main characteristics of masitinib, which of the following is correct?
   a. Masitinib inhibits wild-type *KIT* but not D816V-mutated *KIT*.
   b. Masitinib is more toxic than imatinib because it is less selective towards tyrosine kinase targets.
   c. Masitinib is currently FDA- and EMA-approved and commercialized.
   d. While not indicated for mastocytosis, masitinib is indicated for MCAS.

5. Regarding midostaurin, which of the following is correct?
   a. Midostaurin is approved for the treatment of indolent systemic mastocytosis with severe mast cell activation symptoms.
   b. Midostaurin has proven effective for control of mast cell mediator–related symptoms, even in patients who whose mast cell burden did not decrease.
   c. Midostaurin does not inhibit mast cell mediator release in vitro.
   d. a and b are correct.

6. Which of the following statements about midostaurin is false?
   a. Midostaurin is approved as monotherapy in adults with advanced forms of mastocytosis.
   b. In vitro studies have shown that midostaurin is active on all common mutated forms of c-kit, except for D816V.
   c. The frequency of response to midostaurin in phase 2 studies was 60%-69%, with a significant decrease in mast cell burden and serum tryptase levels.
   d. Gastrointestinal adverse effects caused by midostaurin are very frequent, and grade 3 or 4 neutropenia, anemia, and thrombocytopenia were observed in 24%-41% of patients, mainly in those with cytopenia at baseline.

7. Which mutation does avapritinib primarily target?
   a. The *KIT* D816V mutation
   b. The *PDGFRA* activation loop mutation
   c. The *BRAF* V600E mutation
   d. The *JAK2* mutation

8. Which of the following is true about the efficacy of avapritinib compared with midostaurin?
   a. Avapritinib has lower survival rates than midostaurin.
   b. Avapritinib improves overall survival and response rates compared to midostaurin.
   c. Avapritinib only reduces symptoms but has no survival benefit.
   d. Midostaurin has better selectivity for D816V-mutated *KIT* than avapritinib.

9. TKIs have been employed in gastrointestinal stromal tumors. With which of the following can bezuclastinib be successfully combined?
   a. Avapritinib.
   b. Imatinib.
   c. Sunitinib.
   d. Ripretinib.

10. Which of the following is not a common adverse effect of bezuclastinib?
    a. Change in hair color.
    b. Taste alterations.
    c. Thrombocytopenia.
    d. Intracranial bleeding.

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