

Systemic Mastocytosis: Current Classification and Novel Therapeutic Options

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Abstract: Systemic mast cell disease is characterized by dysregulated mast cell growth and survival, with infiltration into multiple organs and release of systemic mediators. Much has been learned about mast cell biology over the past 20 years, and it has become apparent that activating mutations in the c-KIT receptor tyrosine kinase underlie the aberrant cell signaling and mast cell growth in a majority of patients. Despite this knowledge, targeted therapy with imatinib has been largely unsuccessful due to resistance of the common c-KIT D816V (Asp-->Val) mutation. Novel strategies designed to inhibit the growth of mast cells containing the c-KIT D816V mutations have shown success in vitro and may provide effective targeted therapy for this treatment-refractory disease.

Mastocytosis is a heterogeneous clinical entity marked fundamentally by a neoplastic proliferation of mast cells with pathologic activation and release of vasoactive mediators. The cutaneous form of mastocytosis was first described in 1869, when Nettleship and Tay identified the classic skin lesions of urticaria pigmentosa, which are small pigmented macules or papules that urticate in response to rubbing or scratching.¹ After discovery of the mast cell in 1879 by Ehrlich,² it was subsequently shown that the lesions of urticaria pigmentosa contain an abundance of mast cells.³ It was not until 1949, when Ellis described an autopsy case of a patient with urticaria pigmentosa and bone marrow involvement, that mastocytosis was associated with systemic disease.⁴

Over the past 20 years much has been learned about mast cell biology and the molecular pathogenesis of mastocytosis. In particular, mast cell development has been shown to rely upon interaction of mast cell growth factor, also known as KIT ligand or stem cell factor, with KIT, a receptor tyrosine kinase found on the mast cell surface. Moreover, activating mutations of c-KIT have been demonstrated to underlie the aberrant mast cell proliferation in a majority of patients with systemic mastocytosis. Unfortunately, targeted therapy with imatinib (Gleevec, Novartis) has not yielded significant results in most cases, due to resistance of the most common

Keywords

Mast cells, systemic mastocytosis, c-KIT, imatinib

Table 1. Diagnostic Criteria for Mastocytosis

<p>Cutaneous Mastocytosis</p> <ol style="list-style-type: none"> 1. Typical clinical signs (UP/MPCM, DCM, mastocytoma) 2. Histology with typical mast-cell infiltrates <p>Systemic Mastocytosis</p> <p><i>Major Criteria</i></p> <ol style="list-style-type: none"> 1. Multifocal dense infiltrates of mast cells (≥ 15 in aggregates) in biopsy of bone marrow and/or 2. Other extracutaneous organs confirmed by tryptase immunohistochemistry or another stain <p><i>Minor Criteria</i></p> <ol style="list-style-type: none"> 1. Mast cell infiltrates contain $>25\%$ spindle-shaped cells in extracutaneous organs or bone marrow sections, or $>25\%$ atypical mast cells (type I plus type II) in bone marrow smears 2. c-KIT D816V mutation present in extracutaneous organ(s) 3. Expression of CD2 and/or CD25 on KIT+ mast cells 4. Serum tryptase >20 ng/mL (not valid for SM-AHNMD) <p>Diagnosis = 1 major and 1 minor criterion or 3 minor criteria</p>
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Consensus proposal derived from the Year 2000 Working Conference on Mastocytosis.⁵

DCM = diffuse cutaneous mastocytosis; MPCM = maculopapular cutaneous mastocytosis; SM-AHNMD = systemic mastocytosis with an associated clonal hematologic non-mast cell lineage disease; UP = urticaria pigmentosa.

c-KIT D816V (Asp \rightarrow Val) mutation; however, a number of recently developed agents have been shown to inhibit the c-KIT D816V mutation in vitro. This review focuses on the potential for such advances to offer therapeutic efficacy in a disease that has traditionally been refractory to treatment.

Classification and Clinical Manifestations of Mast Cell Disease

Mast cell disorders were recently reclassified by the World Health Organization (WHO) based upon a consensus proposal derived from the Year 2000 Working Conference on Mastocytosis.^{5,6} Patients with urticaria pigmentosa and histologic evidence of mast cell infiltration of the skin without systemic involvement are classified as having cutaneous mastocytosis (CM). A majority of such patients are children, and lesions tend to develop early in childhood and resolve at the time of puberty, with a benign clinical course.^{7,8} Lesions exhibit the classic urticarial reaction in response to rubbing or scratching, known as Darier's sign. Histologically, mast cells can be identified on skin biopsy

using metachromatic stains such as Giemsa or toluidine blue, and by immunohistochemical staining for tryptase.⁹ Several rare variants of CM include diffuse CM with a generalized erythrodermic rash, solitary mastocytoma of the skin, and telangiectasia macularis eruptiva perstans, a telangiectatic subvariant.¹⁰

Systemic mastocytosis (SM) is associated with infiltration of mast cells into organs such as the liver, spleen, lymph nodes, gastrointestinal tract, and skin, as well as bone and bone marrow. Release of systemic mediators such as histamine can result in symptoms such as flushing, pruritis, and anaphylaxis, as well as diarrhea, cramping, abdominal pain, and peptic ulceration from gastric hypersecretion. The degree of systemic involvement has been stratified by the presence of so-called B and C findings. The B findings include a high mast cell burden characterized by an elevated serum tryptase level (>200 ng/mL), dysmyelopoiesis, and organomegaly; the C findings include evidence of impaired organ function, such as hepatomegaly with portal hypertension or ascites, splenomegaly with hypersplenism, malabsorption with hypoalbuminemia, peripheral cytopenias, and diffuse bony involvement with osteolytic lesions, osteoporosis, or pathologic fractures.⁵

The WHO diagnostic criteria and a new classification scheme for SM were proposed based upon advances in laboratory-based markers for mast cell disease and development of previous systems of classification.⁵ One of the hallmarks of systemic involvement is infiltration of the bone marrow by mast cells in aggregates over 15 in number, with an atypical and spindle-shaped appearance, adjacent to endosteal surfaces.^{11,12} Flow cytometric analysis reveals that mast cells in patients with SM, in addition to being positive for surface expression of c-KIT (CD117), are also positive for the aberrant expression of CD2 and/or CD25.^{13,14} Serum tryptase measurement correlates with total mast cell burden in SM but is normal or only slightly elevated in patients with CM.^{15,16} These developments, in addition to identification of the c-KIT D816V mutation, have been incorporated into the consensus criteria for the diagnosis of systemic mastocytosis (Table 1).⁵ Diagnosis of SM requires one major and one minor criterion, or three minor criteria.

Traditional classification of mast cell disease has included four broad categories: an indolent form, a form associated with malignancy or hematologic disease, an aggressive variant, and mast cell leukemia or malignancy.¹⁷ This classification was standardized by the consensus proposal and the WHO and now includes indolent SM (ISM), SM with an associated clonal hematologic non-mast cell lineage disease (SM-AHNMD), aggressive SM (ASM), mast cell leukemia (MCL), and the rare variants mast cell sarcoma and extracutaneous mastocytoma

(Table 2).^{5,6} Lack of B or C findings is consistent with ISM, whereas the presence of any C finding is consistent with ASM. Isolated B findings are consistent with an ISM variant termed smouldering SM (SSM). The presence of more than 20% mast cells in the bone marrow with over 10% mast cells in the peripheral blood is consistent with MCL. An aleukemic variant of MCL with more than 20% mast cells in the bone marrow with less than 10% mast cells in the peripheral blood is also described.

The presence of an associated clonal hematologic non–mast cell lineage disease defines SM-AHNMD, and such associated disorders can be myeloid, or rarely lymphoid.^{18,19} Cases of SM associated with myeloproliferative disease (MPD), myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML), non-Hodgkin lymphoma, and multiple myeloma have all been described and are classified separately according to WHO criteria.²⁰⁻²⁴ For the most part, such disorders are considered distinct and treatment is directed at each individual underlying hematologic disorder. However, patients with a particular variant—SM associated with chronic eosinophilic leukemia (SM-CEL), alternatively described as the myeloproliferative variant of hypereosinophilic syndrome (HES) or systemic mast cell disease with eosinophilia (SCMD-eos)—possess a unifying clonal abnormality with important therapeutic implications.²⁵⁻²⁸

Systemic Mastocytosis Associated With Chronic Eosinophilic Leukemia

Eosinophilia is frequently associated with systemic mast cell disease; it is detected in the peripheral blood and bone marrow in approximately 20% of patients in some series and up to 33% in others.^{29,30} Insight into the etiology of a specific variant of SM associated with a primary eosinophil disorder arose from studies of the idiopathic HES. Treatment of a small number of HES patients with imatinib, an inhibitor of the BCR-ABL, platelet-derived growth factor receptor (PDGFR)- α and - β , and c-KIT kinases, led to complete hematologic responses in 4 of 5 patients.³¹ This observation led to the cloning of the *FIP1L1-PDGFR* fusion gene in patients with HES responsive to imatinib.²⁵ This fusion product is generated by an interstitial deletion on chromosome 4q12, which contains the cysteine-rich hydrophobic domain 2 (CHIC2) locus.²⁵

The *FIP1L1-PDGFR* fusion is present in some patients with SM-CEL.^{26,27} In one study, deletion of CHIC2, a surrogate for *FIP1L1-PDGFR* fusion, was observed in bone marrow cells of 3 of 5 patients, whereas the other 2 patients carried the c-KIT D816V mutation.²⁶ Therapeutic response to imatinib correlated with the presence of the *FIP1L1-PDGFR* fusion, but not the c-KIT D816V mutation. In another study, a similar variant of

Table 2. Classification of Mastocytosis

<p>Cutaneous Mastocytosis</p> <ul style="list-style-type: none"> • Urticaria pigmentosa/maculopapular cutaneous mastocytosis • Diffuse cutaneous mastocytosis • Mastocytoma of the skin • Telangiectasia macularis eruptiva perstans <p>Indolent Systemic Mastocytosis</p> <ul style="list-style-type: none"> • Smouldering systemic mastocytosis • (Isolated) bone marrow mastocytosis <p>Systemic Mastocytosis with an Associated Clonal Hematologic Non–Mast Cell Lineage Disease</p> <ul style="list-style-type: none"> • Systemic mastocytosis—myelodysplastic syndrome • Systemic mastocytosis—myeloproliferative disorder • Systemic mastocytosis—chronic eosinophilic leukemia • Systemic mastocytosis—acute myeloid leukemia • Systemic mastocytosis—non-Hodgkin lymphoma • Systemic mastocytosis—multiple myeloma <p>Aggressive Systemic Mastocytosis</p> <p>Mast Cell Leukemia (MCL)</p> <ul style="list-style-type: none"> • Classical MCL • Aleukemic variant of MCL <p>Mast Cell Sarcoma</p> <p>Extracutaneous Mastocytoma</p>

World Health Organization (WHO)/Consensus proposal derived from the Year 2000 Working Conference on Mastocytosis.^{5,6}

SM-CEL disease was identified by lack of c-KIT mutation, the presence of the *FIP1L1-PDGFR* fusion, and elevated serum tryptase levels.²⁷ Such patients typically exhibited clinical and hematologic responses to imatinib. A subsequent study examining treatment of 7 patients with SM-CEL with imatinib demonstrated significant clinical improvement in all patients and molecular remission determined by absence of the *FIP1L1-PDGFR* fusion transcript in 5 of 6 patients tested.³²

A large, combined prospective and retrospective analysis of patients with HES and SM-CEL was carried out to determine the prevalence of the *FIP1L1-PDGFR* fusion and its clinicopathologic correlates.³³ Whereas none of the 57 patients with a clinical diagnosis of HES had the fusion gene, 10 of 19 patients (56%) with SM-CEL carried the *FIP1L1-PDGFR* fusion. The authors concluded that in patients who meet diagnostic criteria for HES, further testing with immunohistochemistry for mast cell markers and measurement of serum tryptase levels may help distinguish the SM-CEL variant. However, it is important to point out that such cases of SM are often associated with an indolent form of disease (ie, ISM)²⁸

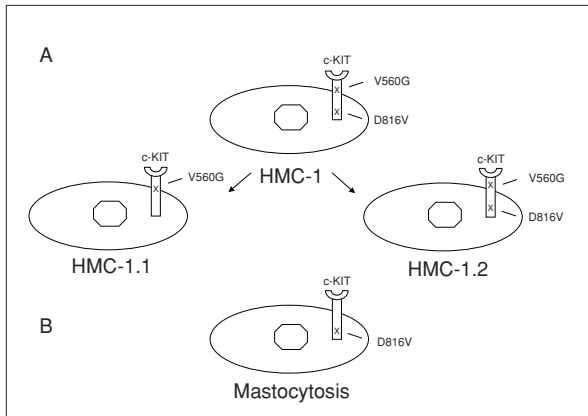


Figure 1. c-KIT mutations in mast cell leukemia cell lines and in patients with mastocytosis.

and that treatment decisions should not simply be based upon the presence of eosinophilia or *FIP1L1-PDGFR* fusion, but upon the final diagnosis and the presence or absence of C findings.

Molecular Regulation of Mast Cell Differentiation and Proliferation

Genetic studies in the 1950s showed that mutation at the steel (Sl) locus in mice results in defective melanocyte, germ cell, and hematopoietic cell development.³⁴ Similar defects were noted to be present in mice with dominant white spotting (W) mutations, so named because of the white skin and hair resulting from abnormal melanocyte development.^{35,36} Studies ultimately demonstrated that these animals are also deficient in mast cells, and that this defect could be corrected by bone marrow transplantation, thus establishing the bone marrow origin of mast cells.³⁷⁻³⁹ The identity of the genes underlying these defects became apparent after the cloning of the *c-kit* proto-oncogene, which was identified as the cellular homolog of the *v-kit* oncogene, found in a transforming feline retrovirus isolated from a feline fibrosarcoma.⁴⁰ The protein product of *c-kit* was found to be a transmembrane tyrosine kinase homologous to the PDGFR and colony-stimulating factor 1 receptor, and the mouse homolog was shown to map to the W locus.⁴¹⁻⁴⁴ Subsequently, a series of elegant experiments demonstrated that a mast cell growth factor (MGF), purified from supernatant of a bone marrow stromal cell line, is a ligand for c-KIT and maps to the Sl locus in mice.⁴⁵⁻⁴⁷ The c-KIT ligand was also shown to be equivalent to stem cell factor (SCF). It is thus variably termed KIT ligand, mast cell growth factor, steel factor, or stem cell factor, depending upon the context in which it is discussed.^{48,49}

Given these findings, patients with CM were examined for expression of SCF. It was demonstrated

that the epidermis and dermis of urticaria pigmentosa lesions contain excess levels suggesting that some forms of mastocytosis might be due to reactive hyperplasia rather than mast cell neoplasia.⁵⁰ On the other hand, serum levels of SCF were found to be the same in patients with mastocytosis and normal individuals, and it was shown instead that CD34-positive cells from patients with aggressive SM differentiate more readily into mast cells in the presence of SCF, suggesting hyperactivity of c-KIT signaling.⁵¹ In addition, molecular analysis of the human mast cell leukemia cell line (HMC-1) revealed constitutive phosphorylation of c-KIT and the presence of two separate mutations, Val560Gly (V560G) and Asp816Val (D816V), the latter of which appeared to be more activating in vitro (Figure 1A).⁵² Subsequently, the c-KIT D816V mutation was identified in patients with mastocytosis, implicating constitutively active c-KIT signaling in the dysregulated growth of mast cells in these patients (Figure 1B).⁵³ Moreover, identification of the c-KIT D816V mutation in mast cells at different sites established the clonality of systemic mastocytosis.⁵⁴ The c-KIT D816V mutation is rarely found in pediatric patients and has been shown to be associated with a more severe disease pattern.⁵⁵ It is present in a majority of adult sporadic cases of systemic mastocytosis, although not in patients with familial mastocytosis.⁵⁶

Consistent with other myeloproliferative disorders, the c-KIT D816V mutation has been identified in an early hematopoietic progenitor cell capable of giving rise both to myeloid and lymphoid cells.^{57,58} It has also been observed in myelomonocytic cells, B cells, and T cells in patients with mastocytosis, but, unlike normal mast cells, these cells lack significant surface expression of c-KIT, potentially explaining the phenotypic consequences of the mutation.⁵⁷ Multilineage involvement has been observed in other studies but was only detected in patients with severe systemic mast cell involvement, suggesting that in patients with more limited disease, the c-KIT D816V mutation may occur in a committed mast cell progenitor.^{58,59} Indeed, in most patients with ISM and all with CM, monocytes and B cells are polyclonal cells that lack c-KIT D816V.

Traditional Therapy of Mast Cell Disease

Therapy for mastocytosis can be divided into treatment of mediator-related symptoms and cytoreductive treatment aimed at reducing mast cell burden. Pathologic degranulation of mast cells is associated with release of systemic mediators such as histamine, prostaglandins (eg, PGD₂), and leukotrienes (eg, LTC₄), as well as a variety of chemokines and cytokines.⁶⁰⁻⁶² Agents used to control symptoms due to mediator release include the mast cell stabilizers cromolyn sodium and ketotifen, as well as histamine

receptor blockers (both H1 and H2).⁶³⁻⁶⁵ More recently, efficacy of the leukotriene receptor inhibitor montelukast has been reported as well.⁶⁶ Topical corticosteroids and psoralen ultraviolet A (PUVA) therapy have been used to treat the lesions of urticaria pigmentosa.^{67,68}

More aggressive treatment is required for patients with evidence of organ dysfunction (C findings) and ASM, SM-AHNMD, or MCL. A variety of cytoreductive and immunomodulatory agents have been tried, but responses are somewhat limited.⁶⁹ Although some of the highest responses for ASM have been seen with interferon (IFN)- α 2b (either with or without corticosteroids), major responses with resolution of C findings have only been seen in 21% of patients.⁷⁰ In a large series of adult SM patients treated with IFN- α , only 65% of patients were able to tolerate at least 6 months of therapy, with an overall partial response rate of 35% and minor response rate of 30%.⁷¹ More recently, therapeutic efficacy of the purine nucleoside analog cladribine has been observed in ASM.⁷² In a pilot study, 9 of 10 patients with various forms of mastocytosis treated with cladribine had partial responses, with one major response.⁷³ In another series, treatment of 4 patients with ASM refractory to IFN- α resulted in major responses in 2 patients and a partial response in another patient, with duration of remission in 1 patient lasting up to 81 months.⁷⁴ Most recently, a French multicenter study of 33 patients reported a major response in 24 patients, with a median duration of response of 16 months.⁷⁵ Patients with MCL or SM-AHNMD with MDS or AML have been treated with AML-type chemotherapy and/or allogeneic stem cell transplantation with variable success.⁷⁶⁻⁷⁸

Imatinib and Systemic Mastocytosis

Imatinib has revolutionized the therapy of chronic myelogenous leukemia (CML) by virtue of its ability to target the BCR-ABL tyrosine kinase.⁷⁹ Furthermore, inhibition of aberrant c-KIT activation in gastrointestinal stromal cell tumors (GISTs) by imatinib has led to significant therapeutic efficacy in this disease as well.⁸⁰ As mentioned above, however, imatinib has not yielded significant responses in patients with SM carrying the c-KIT D816V mutation, instead it has shown activity only in the smaller subset of patients with wild-type or other c-KIT variants, and in SM-CEL in the presence of the *FIP1L1-PDGFR*A fusion.^{26,27,32,81}

The molecular basis for imatinib resistance of the c-KIT D816V mutation has been demonstrated in vitro.⁸² Mutations in c-KIT can be divided into those that directly involve the enzymatic pocket and affect the activation loop (eg, D816V) and those that involve the juxtamembrane regulatory region and disrupt an inhibitory amphipathic helix (eg, V560G) (Figure 2).⁸³ A majority of the c-KIT

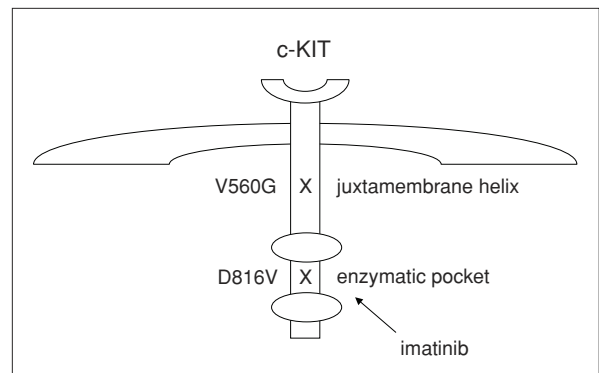


Figure 2. Major classes of c-KIT mutations in systemic mastocytosis.

mutations found in GISTs involve the juxtamembrane regulatory region, with most mutations occurring between exons 550 and 560.⁸⁴ Thus, sensitivity of GISTs to imatinib can be explained by the fact that the c-KIT active site to which the drug binds is rarely mutated, except with the development of imatinib resistance.⁸⁵

In contrast, the c-KIT D816V mutation found in a majority of patients with systemic mastocytosis directly affects the kinase domain to which imatinib binds. As explained above, the human mast cell leukemia cell line HMC-1, in which the c-KIT D816V mutation was originally identified, also contains a V560G mutation and thus exhibits both classes of c-KIT mutations (Figures 1 and 2). In vitro, both the V560G and D816V c-KIT mutations exhibit constitutive activation and autophosphorylation, but only the V560G mutation is inhibited by imatinib.⁸² In addition, a subclone of the HMC-1 cell line that contains only the c-KIT V560G mutation (HMC-1.1) is inhibited by imatinib, whereas cells possessing both the V560G and D816V mutation (HMC-1.2) are insensitive to imatinib.^{82,86} More recently, novel germline mutations have been described in the transmembrane domain of c-KIT in an imatinib-sensitive variant of mastocytosis, without involvement of the kinase domain, providing further support for the notion that activating mutations outside of the enzymatic pocket retain sensitivity to imatinib, in contrast to the D816V mutation.^{87,88} It must be noted, however, that much of the work demonstrating resistance of c-KIT D816V to imatinib has been performed in vitro. Indeed, preliminary results from a phase I/II trial in the Netherlands have shown partial responses with imatinib in a number of SM patients carrying the D816V mutation.⁸⁹

Novel Targeted Therapy for Mast Cell Disease

Over the past several years, it has become apparent that resistance to imatinib in CML is often due to mutations

in the BCR-ABL kinase domain, interfering with drug binding.⁹⁰ In an attempt to overcome this resistance, novel compounds such as dasatinib (Sprycel, Bristol-Myers Squibb) and nilotinib (Novartis) have been developed, which are more potent inhibitors of BCR-ABL and thus inhibit activity of most BCR-ABL mutants that are insensitive to imatinib.^{91,92} In addition, a novel staurosporine-derived tyrosine kinase inhibitor, PKC412 (Novartis), which has been shown to inhibit the Fms-like tyrosine kinase (FLT3), c-KIT, and PDGFRA, among other targets, has been shown to overcome imatinib resistance in a murine model of *FIP1L1-PDGFR*A-induced myeloproliferative disease.⁹³

The ability of such compounds to inhibit mutated tyrosine kinase domains resistant to imatinib has prompted a number of investigators to test for activity of these drugs against the c-KIT D816V mutation. Two groups independently showed that dasatinib can inhibit the c-KIT D816V mutation with high nanomolar activity and induce apoptosis of several mastocytosis cell lines.^{94,95} In addition, in contrast to imatinib, nilotinib has been found to inhibit the growth of Ba/F3 cells engineered to express the c-KIT D816V mutation.⁹⁶

In a similar fashion, activity of PKC412 has been tested against a variety of c-KIT mutations, including D816V, in Ba/F3 cells.⁹⁷ PKC412 was found to be an extremely potent inhibitor of the c-KIT D816V mutation compared to imatinib, with a 50% minimal inhibitory concentration of 44 nM for PKC412 compared with 10,651 nM for imatinib, a 242-fold increase in potency. Given these findings, PKC412 was used to treat a patient with SM-AHNMD (MDS/MPD) with progression to MCL.⁹⁸ Treatment was associated with marked clinical improvement, a reduction of circulating mast cells from 46% to less than 5%, as well as a significant decline in histamine levels and bone marrow mast cells. Despite persistent efficacy against the MCL, the patient subsequently developed transformation of the MDS/MPD component into AML and ultimately died. Although this response was seen in only 1 patient, the efficacy of PKC412 in this case seemed promising; a multicenter trial using PKC412 for mastocytosis is currently enrolling patients.

Recently, *in vitro* activity of PKC412 has been compared with that nilotinib, imatinib, and cladribine against mast cells expressing the c-KIT D816V mutation.⁹⁹ Whereas imatinib failed to inhibit autophosphorylation of the c-KIT D816V mutation, similar concentrations of PKC412 and nilotinib decreased c-KIT phosphorylation, although nilotinib did so to a lesser degree than PKC412. In addition, effects of these compounds were examined in HMC-1.1 cells, which contain the juxtamembrane c-KIT V560G mutation alone, and in HMC-1.2 cells, which also contain the D816V mutation (Figure 1). All three drugs were effective in inhibiting the growth

of HMC-1.1 cells, with nilotinib appearing to be the most potent in this setting. However, PKC412 was the most potent inhibitor of growth of HMC-1.2 cells, with no effect by imatinib, and a weaker effect by nilotinib. Moreover, apoptosis of HMC-1.2 cells was more marked in cells treated with PKC412 compared with nilotinib, with no apoptosis observed following treatment with imatinib. Interestingly, the combination of PKC412 with nilotinib or with cladribine produced synergistic effects in HMC-1.1 cells and additive effects in HMC-1.2 cells, with enhanced growth inhibition in both settings. These findings provide further support for a role of PKC412 and nilotinib in the treatment of SM, and suggest that combination therapy with each other or with cladribine may enhance efficacy.

Another recent advance is the observation that rapamycin (Rapamune, Wyeth) specifically inhibits the growth of mast cells containing the c-KIT D816V mutation.¹⁰⁰ This study was prompted by the observation that signaling through the c-KIT D816V mutation is dependent upon STAT3 activation as well as downstream activation of the mammalian target of rapamycin (mTOR).¹⁰¹ Treatment with rapamycin resulted in the inhibition of mTOR substrates and induction of apoptosis in c-KIT D816V-positive mast cells, but not in normal mast cells or in HMC-1 cells containing the c-KIT V560G mutation alone.¹⁰⁰ These results suggest potential therapeutic efficacy for rapamycin or its derivatives in c-KIT D816V-positive systemic mastocytosis.

Conclusion

There has been a dramatic gain in understanding of the basic molecular biology of mast cell disease over the past 20 years, leading to an improved classification system for mast cell disorders and identification of subsets of patients responsive to specific therapies. However, at the present time, therapy of mast cell disease remains largely symptom-driven and nonspecific, with immunologic agents such as IFN and improved cytotoxic agents such as cladribine being the principal options. Initial attempts at therapy with targeted agents such as imatinib have been largely unsuccessful, except in the SM-CEL variant of disease. The identification of novel tyrosine kinase inhibitors that target and inhibit the c-KIT D816V mutation, which is responsible for the aberrant mast cell proliferation in most cases, yields great promise for targeted therapy for this disorder. Drugs such as PKC412, nilotinib, and dasatinib have all demonstrated superior efficacy to imatinib *in vitro*, inhibiting the growth and inducing apoptosis of mast cell lines that contain this pathogenic mutation. Initial clinical experience with these drugs in the treatment of other hematologic disorders such as AML and CML has revealed excellent oral bioavailability and relatively mod-

est side effect profiles, similar to imatinib. Several clinical trials are currently underway to determine the efficacy of these agents in the treatment of patients with systemic mastocytosis. If these trials are successful, mastocytosis will provide an elegant example of how understanding the molecular pathogenesis of disease can translate into effective clinical care.

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