Drugs of the Future 2008, 33(2): 187-192

CCC: 0377-8282/2008
DOI: 10.1358/dof.2008.033.02.1180805

Systemic mastocytosis+

Nitin Jain, Srdan Verstovsek*
Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA.
**Correspondence: sverstov@mdanderson.org*

CONTENTS

Abstract

Mastocytosis is a heterogeneous group of disorders characterized by clonal expansion of mast cells. Clinical course can range from no or minimal symptoms to diffuse systemic involvement with multiorgan failure. The diagnosis of systemic mastocytosis primarily relies on the identification of neoplastic mast cells (spindle-shaped cells expressing CD2/CD25) in various organs, especially the bone marrow. Serum tryptase and urinary histamine levels are typically elevated. There is no effective treatment for systemic mastocytosis. Most patients are treated with antihistamines for symptom control. For patients with aggressive disease, cytoreductive therapy with interferon alfa or cladribine is indicated. The *KIT* gene D816V mutation is present in approximately 90% of patients and several medications targeting this *KIT* mutant are currently being investigated. As no established treatment regimen exists, enrollment into a clinical trial should be strongly considered.

Introduction

Mastocytosis is a heterogeneous group of disorders characterized by clonal expansion of mast cells (MCs) and their excessive accumulation in various organs, such as the skin, bone marrow, gastrointestinal tract, lymph nodes, liver and spleen. The clinical course can range from no or minimal symptoms to diffuse systemic involvement with multiorgan failure.

Mastocytosis has been classified into seven subtypes according to the 2001 World Health Organization (WHO) guidelines: cutaneous mastocytosis, indolent systemic mastocytosis (ISM), SM with an associated clonal hematological non-MC lineage disease (SM-AHNMD), aggressive SM (ASM), MC leukemia, MC sarcoma and extracutaneous mastocytoma (1, 2). SM is defined by the presence of one major and one minor or three minor diagnostic criteria (Table I) (1). Patients with SM are further characterized with regard to the presence of so-called "B and C findings" (assessing disease burden and disease aggressiveness, respectively) (Table II). SM patients with no findings are identified as ISM, those with B findings as smoldering SM (SSM, a subtype of ISM with a possibly more aggressive clinical course) and those with C findings as ASM (2, 3). New WHO guidelines due out this year redefine mastocytosis as "mast cell disease" with SM, a subtype with bone marrow involvement (4, 5).

Clinical manifestations

Symptoms of mastocytosis can be divided into those due to MC mediator release and those due to MC organ infiltration.

Symptoms of mediator release

Vasoactive mediators (histamine, leukotrienes, heparin, prostaglandins) released from MCs can lead to itching, flushing, lightheadedness, syncope, palpitations, diarrhea, heartburn, fatigue and headache. MC degranulation can be exacerbated by infections, alcohol, exercise and medications.

Symptoms of organ infiltration

Skin involvement can occur as cutaneous mastocytosis or as cutaneous manifestations of SM. Urticaria pigmentosa is the most common skin manifestation, characterized by reddish-brown macules and papules. Nodular and plaque-like lesions can occur. Associated pruritus is exacerbated by local friction, spicy food and temperature changes. Scratching of affected skin characteristically leads to the development of urticaria and erythema (Darier's sign). Gastrointestinal involvement can present as chronic diarrhea, steatorrhea, malabsorption and ascites. Anemia is the most common hematological

+ See also: Kit mutations in cancer and their treatment with protein kinase inhibitors, p 161 this issue.

Table I: World Health Organization diagnostic criteria for systemic mastocytosis.

Major criteria

1. Multifocal, dense infiltrates of mast cells (15 mast cells in aggregates) in bone marrow biopsy sections and/or in other extracutaneous organ(s)

Minor criteria

1. Greater than 25% mast cells in bone marrow or other extracutaneous organ(s) show an atypical morphology (typically spindle-shaped)
2. *KIT* mutation at codon 816 is present in extracutaneous tissues
3. Mast cells in bone marrow co-express CD117 and either CD2 or CD25, or both (by flow cytometry)
4. Serum tryptase persistently is ≥ 20 ng/ml (not accounted for in patients with an associated clonal, hematological, non-mast cell disorder)

A diagnosis of systemic mastocytosis requires the fulfillment of either one major criteria and one minor criteria or three minor criteria.

Table II: B findings and C findings in systemic mastocytosis.

B findings: indication of high mast cell burden and expansion of the genetic defect into various myeloid lineages

1. Infiltration grade of mast cells in bone marrow > 30% on histology and serum total tryptase levels > 200 ng/ml
2. Hypercellular bone marrow with loss of fat cells, discrete signs of dysmyelopoiesis without substantial cytopenias, or World Health Organization criteria for myelodysplastic syndrome or myeloproliferative disorder
3. Organomegaly: palpable hepatomegaly, splenomegaly or lymphadenopathy (> 2 cm on computed tomography or ultrasound) without impaired organ function

C findings: indication of impaired organ function because of mast cell infiltration (confirmed by biopsy in most patients)

1. Cytopenia(s): absolute neutrophil count < 1000/μl or hemoglobin < 10 g/dl or platelets < 100,000/μl
2. Hepatomegaly with ascites and impaired liver function
3. Palpable splenomegaly with hypersplenism
4. Malabsorption with hypoalbuminemia and weight loss
5. Skeletal lesions: large osteolyses or/and severe osteoporosis causing pathological fractures
6. Life-threatening organomegaly in other organ systems that is definitively caused by an infiltration of the tissue by neoplastic mast cells

abnormality due to bone marrow infiltration and peripheral eosinophilia is seen in around 20% of patients (6). Bone pain and fractures can occur as a result of MC mediator-induced abnormal bone turnover or due to direct destruction of the bones by invading MCs (7).

Diagnosis

The diagnosis of SM is based on a set of diagnostic criteria (Table I) but primarily relies on the identification of neoplastic MCs in various organs. Bone marrow examination is imperative for SM diagnosis, as most adults with mastocytosis have underlying bone marrow involvement. Bone marrow examination also helps diagnose any underlying AHNMD. Neoplastic MCs are characteristically spindle-shaped and present in multifocal aggregates (8). Unlike normal MCs, neoplastic MCs express the surface markers CD2 and/or CD25 (9). Serum tryptase and urinary histamine levels (both released by MCs) are typically elevated. *KIT* gene D816V mutation screening should be considered for all patients as it is present in approximately 90% of SM patients.

Conventional treatment

There is a lack of effective treatment for SM. Standard treatment for SM has been aimed at symptom control. This includes the use of oral antihistamines and MC stabilizers like cromolyn sodium (2, 10). Patients should avoid specific factors that can trigger MC degranulation, such as emotional stress, cold exposure, alcohol use, strenuous exercise and the use of nonsteroidal antiinflammatory drugs. Both sedating (hydroxyzine, diphenhydramine) and nonsedating second-generation H_1 antihistamines (cetirizine, loratadine, desloratadine, fexofenadine) can be used to alleviate pruritus and itching. However, randomized controlled trials (RCTs) evaluating the comparative efficacy of antihistamines in SM are lacking.

Cetirizine has been shown to be equivalent to hydroxyzine in relieving pruritus in RCTs in patients with chronic urticaria, with the advantage of a lack of sedation and less frequent daily dosing (11, 12). Most patients, therefore, are initially treated with nonsedating H_1 antihistamines. For some patients with severe symptoms of urticaria, higher doses of sedating antihistamines could

be more effective. As both H_1 and H_2 receptors are present in skin (85% of cutaneous histamine receptors are H_1 and 15% are H_2), the addition of an H_2 blocker (ranitidine, famotidine) should be considered for patients not responding to H_1 antihistamines alone (11).

Cromolyn sodium has been shown to be beneficial in patients with gastrointestinal symptoms (diarrhea, vomiting, abdominal pain). In a trial in 10 patients, cromolyn sodium was also shown to be equivalent in terms of symptom alleviation to a combination of chlorpheniramine and cimetidine in patients with mastocytosis (13). Short courses of prednisone can be considered for patients with severe symptoms not controlled with other supportive medications, or for those with malabsorption and ascites (14). Aspirin can be used to decrease flushing, although aspirin use by itself can lead to MC degranulation. It is recommended that patients should be on H_1 and H_2 antihistamine prophylaxis before undertaking aspirin therapy. Topical cromoglycates, topical corticosteroids and PUVA (psoralen-ultraviolet A) therapy have been used for some patients with cutaneous manifestations (10). Patients with a history of anaphylaxis or cardiovascular collapse should carry an epi-pen for epinephrine self-administration. Omalizumab, a humanized murine monoclonal antibody that inhibits immunoglobulin E binding to MCs and basophils, has recently been shown to be of benefit in patients with syncopal episodes related to mastocytosis (15) and for SM cutaneous manifestations (16). For patients with osteoporosis, bisphosphonate therapy (pamidronate 90 mg i.v. monthly) should be considered (5). Other treatments that have been used for SM are cytoreductive medications, including interferon alfa and cladribine. Novel treatments targeting the mutated Kit tyrosine kinase are being investigated in clinical studies (see below). Cytoreductive therapies are usually reserved for patients with ASH, or occasional patients with ISH with uncontrolled symptoms or with severe osteoporosis.

Interferon alfa

Interferon alfa has been evaluated for patients with SM by several investigators (17-19). Casassus *et al.* reported a multicenter trial in 20 patients with SM (16 ASM, 4 ISM) treated with interferon alfa-2b (starting dose of 1 million units s.c. daily, escalated to 5 million units/m^2/day depending on tolerance). Thirteen patients (65%) who completed 6 months of treatment responded (7 partial, 6 minor and 0 complete responses). Decreases in plasma histamine and tryptase levels were noted in patients with flushing and gastrointestinal tract symptoms. However, many patients experienced undesirable side effects. Major side effects leading to treatment discontinuation included depression and cytopenias (18). Combination of interferon alfa-2b plus prednisone has been evaluated in a study in 4 SM patients, where 2 patients achieved a complete and 1 patient achieved a partial resolution of C findings (19). Clinical improvement in cutaneous manifestations of SM and osteoporosis has also been documented with interferon treatment.

Cladribine

Few reports have documented the efficacy of cladribine in SM (20, 21). In a multicenter study, all 10 patients treated with cladribine (0.13 mg/kg/day for 5 days repeated every 4-6 weeks) showed improvement in MC-mediated signs and symptoms (20). In the largest series so far of 33 patients, the use of cladribine led to a major response in 24 patients and a minor response in another 2 patients (21). In this study, the mean time to best response was 4 months and the mean duration of response was 16 months. Myelosuppression is the main treatment-related side effect in patients treated with cladribine (20, 21).

Investigational therapies

Kit is a tyrosine kinase receptor encoded by the *KIT* gene located on chromosome 4q12 in humans (22). Binding of stem cell factor (SCF, Kit ligand) to Kit leads to receptor dimerization and phosphorylation of downstream signaling molecules (23). Kit plays an important role in normal hematopoiesis and Kit expression declines in hematopoietic cell lines with maturation, except in MCs. Furitsu *et al.* were the first to show that Kit was constitutively activated and expressed in the absence of SCF in an MC line derived from an MC leukemia patient (24). A point mutation, D816V (substitution of valine for aspartate at codon 816, Asp816Val), in the tyrosine kinase domain of the Kit receptor, first described by Nagata *et al.* (25), has been identified in > 90% of adult patients with SM using a sensitive PCR-based assay (26). Other *KIT* mutations involving tyrosine kinase, juxtamembrane and transmembrane domains have been described in sporadic cases (27). Several medications targeting the *KIT* mutants are currently being investigated as therapy for SM.

Imatinib

Imatinib is a potent inhibitor of various tyrosine kinases, including wild-type Kit (28). However, *in vitro* studies have shown that imatinib is not effective against the most common *KIT* mutation in SM, D816V (29). This is probably due to the fact that imatinib is able to bind Kit only in the inactive configuration and the D816V mutation leads to stabilization of the active open configuration of Kit (27). Clinical experience with imatinib has corresponded to the *in vitro* data, with no significant responses in patients with the *KIT* D816V mutation (30).

Pardanani *et al.* reported 10 SM patients who were treated with imatinib, 2 of whom with the *KIT* D816V mutation did not respond (30). In another study in 14 patients with SM, imatinib at 400 mg daily (with prednisone 30 mg daily for the first 2 weeks) was shown to be beneficial in patients with both mutated *KIT* D816V and wild-type *KIT*. However, prednisone use (an active agent on its own) for the initial 2 weeks might have contributed to the efficacy of imatinib seen in this study (31). Sporadic *KIT* mutations (F522C, K509I, V560G and del419) have been shown to be imatinib-sensitive in isolated cases

(27). Imatinib at a dose of 400 mg daily is approved by the U.S. Food and Drug Administration for adult patients with ASM without the *KIT* D816V mutation, or with unknown *KIT* mutational status.

An important subgroup of SM patients with imatinib responsiveness is the group with an FIP1-like 1-platelet-derived growth factor receptor alpha (*FIP1L1-PDGFRA*) mutation. Peripheral blood eosinophilia is seen in approximately 20% of SM patients (SM-eos) and bone marrow eosinophilia has been reported in 19-33% of SM patients (6). In a study by Pardanani *et al.,* 56% of SM patients with eosinophilia (10 of 19 patients) had the *FIP1L1-PDGFRA* fusion oncogene (32). In this study, all treated SM-eos patients with the *FIP1L1-PDGFRA* mutation (n=7) responded to imatinib 100 mg/day, while those SM-eos patients without the *FIP1L1-PDGFRA* mutation (n=5) did not respond (irrespective of *KIT* D816V mutation status). In another study, 3 of the 5 SM-eos patients with an *FIP1L1-PDGFRA* mutation responded to imatinib (33). It is highly recommended that all patients suspected to have SM-eos undergo testing for the *FIP1L1-PDGFRA* mutation. For patients with this mutation, imatinib 100 mg/day is the treatment of choice. Imatinib is currently approved in the U.S. for patients with ASM associated with eosinophilia (starting dose of 100 mg/day with dose escalation to 400 mg/day if insufficient response and absence of side effects).

Dasatinib

Dasatinib is a dual SRC-ABL inhibitor that is 300-fold more potent than imatinib against BCR-ABL. Dasatinib also inhibits the kinase activity of wild-type *KIT* approximately 20-fold more efficiently than imatinib (34). Most importantly, dasatinib inhibits the kinase activity of *KIT* D816V with comparable efficacy to against wild-type *KIT*. Dasatinib inhibited Kit phosphorylation in MC lines bearing different *KIT* mutations at low nanomolar levels (34).

Based on these exciting preclinical results, a phase II trial of dasatinib in SM was recently conducted and results reported (35). Thirty-three patients were treated (18 with ISH, 9 with ASH and 6 with SM-AHNMD). The dasatinib dose was 70 mg orally twice daily (9 patients received 140 mg once daily). The median age of the patients was 57 years (range: 29-74) and all patients were *PDGFRA*-negative. The median number of prior therapies was 1 (range: 0-4), with 16 patients previously untreated. The median number of cycles received was 4 (range: 1-20, 1 cycle = 4 weeks). Disappointingly, only 2 patients achieved CR: 1 with SM-myelofibrosis (*JAK2* V617F-positive and complex cytogenetics) and 1 with SM-eos. Both patients were *KIT* D816V mutation-negative. The SM-myelofibrosis patient progressed to acute myeloid leukemia (AML) after 8 months on treatment and died, and the SM-eos patient is still in CR after more than 18 months of treatment. Nine additional patients had improvement in symptoms related to SM lasting from 3 to more than 18 months. Nineteen grade 3 toxicities were observed, but no grade 4 toxicity.

PKC-412

PKC-412 (midostaurin) is an *N*-benzoyl-staurosporine with potent inhibitory activity against protein kinase C (PKC), FLT3, PDGF-R-α, VEGFR-2 and Kit. In Ba/F3 cells transfected with *KIT* D816V, PKC-412 led to cellular growth inhibition, with an IC_{50} of 44 nM (36). In experiments in human MC lines bearing different *KIT* mutations, PKC-412 at low micromolar concentration led to decreased phosphorylation of Kit. Similar growth inhibition was noted when primary neoplastic bone marrow-derived MCs from a patient with SM carrying the *KIT* D816V mutation were exposed to PKC-412 (37).

The first report of clinical experience with PKC-412 in SM was in a single patient with MC leukemia and AHNMD with the *KIT* D816V mutation who had a significant decrease in peripheral blood MC burden and serum histamine levels (37). In contrast to peripheral blood, the bone marrow response was minimal and the patient died 3 months after starting PKC-412 due to AHNMD progression.

Preliminary results of a phase II trial using PKC-412 were recently reported (38). Fifteen patients (60% with *KIT* D816V mutations) were treated with PKC-412 at a dose of 100 mg twice daily. A response was achieved in 11 patients (major response in 5 patients and partial response in 6 patients). Two patients had disease progression. In 4 patients, the marrow MC burden decreased from 50-60% to 10-15%. There was an inconsistent decrease in serum tryptase among responding patients.

Nilotinib

Nilotinib (AMN-107) is a phenylaminopyridine that is 20-30 times more potent than imatinib against BCR-ABL. Nilotinib effectively suppressed the growth of mouse Ba/F3 cells transfected with *KIT* D816V at low micromolar concentrations (39). At 1 μM, nilotinib strongly inhibited Kit phosphorylation in the human MC (HMC) line 1.1 (not carrying the *KIT* D816V mutation), but showed only weak effects in the HMC line 1.2 (carrying the *KIT* D816V mutation) (40, 41). Similarly, nilotinib induced apoptosis in the HMC line 1.1, and to a lesser degree in the HMC line 1.2. Verstovsek *et al.* compared the effects of nilotinib and imatinib in the HMC lines 1.1 and 1.2. They reported that in the HMC line 1.1, nilotinib is as potent as imatinib in inhibiting cellular proliferation, with IC_{50} values of 108 and 74 nM, respectively, while in the HMC line 1.2 neither medication had an effect (42). Nilotinib at concentrations up to 1 μM had no effect on bone marrow MCs carrying the *KIT* D816V mutation obtained from patients with SM. In a phase II study, 23 SM patients were treated with nilotinib (400 mg orally twice daily) (43). Three (13%) responses were reported (2 incomplete remissions and 1 minor response), based on serum tryptase, bone marrow MC infiltration and improvement of clinical symptoms.

Many other agents have been studied in preclinical models as possible therapy for SM. These include the

tyrosine kinase inhibitors tandutinib (MLN-518), PD-180970, AP-23464/AP-23848, OSI-930, EXEL-0862, sunitinib and sorafenib, and the nontyrosine kinase inhibitors 17-AAG, IMD-0354 and rapamycin (sirolimus) (27). Nilotinib has shown synergistic activity when combined with PKC-412 (40). Similarly, PKC-412 and dasatinib have been shown to act in synergy in preclinical studies (41), suggesting the potential of combination treatment. Denileukin diftitox, a DNA-derived cytotoxic protein composed of the amino acid sequences of diphtheria toxin fragments A and B and the sequence for interleukin-2 (IL-2), was reported not to be effective clinically in 8 patients with SM (44).

Conclusions

The following conclusions can be reached for the treatment of SM:

- All symptomatic patients should receive H_1 blockers. If symptoms are not controlled, an H_2 blocker can be added.
- For patients with ISM, symptomatic treatment with antihistamines only is usually sufficient. Cytoreductive therapy is not required as disease course is nonprogressive and survival is not affected.
- For patients with ASM, cytoreductive therapy is indicated. Enrollment into a clinical trial should be strongly considered for these patients as no established treatment regimen exists. Outside of a clinical trial, therapy with interferon alfa or cladribine should be considered. All patients suspected to have SM-eos should undergo testing for the *FIP1L1-PDGFRA* mutation and, if present, imatinib (100 mg/day) is the recommended treatment.
- Patients with SM-AHNMD should receive treatment for the associated hematological condition along with symptomatic SM-directed treatment.
- Patients with MC leukemia are typically treated with AML-type chemotherapy regimens. These patients have a uniformly poor prognosis.

References

1. Valent, P., Horny, H.P., Escribano, L. et al. *Diagnostic criteria and classification of mastocytosis: A consensus proposal.* Leuk Res 2001, 25(7): 603-25.

2. Valent, P., Akin, C., Escribano, L. et al. *Standards and standardization in mastocytosis: Consensus statements on diagnostics, treatment recommendations and response criteria*. Eur J Clin Invest 2007, 37(6): 435-53.

3. Valent, P., Akin, C., Sperr, W.R., Horny, H.P., Metcalfe, D.D. *Smouldering mastocytosis: A novel subtype of systemic mastocytosis with slow progression.* Int Arch Allergy Immunol 2002, 127(2): 137-9.

4. Tefferi, A., Vardiman, J.W. *Classification and diagnosis of myeloproliferative neoplasms: The 2008 World Health Organization criteria and point-of-care diagnostic algorithms.* Leukemia 2008, 22(1): 14-22.

5. Tefferi, A., Verstovsek, S., Pardanani, A. *How we diagnose and treat WHO-defined systemic mastocytosis in adults.* Haematologica 2008, 93(1): 6-9.

6. Lawrence, J.B., Friedman, B.S., Travis, W.D., Chinchilli, V.M., Metcalfe, D.D., Gralnick, H.R. *Hematologic manifestations of systemic mast cell disease: A prospective study of laboratory and morphologic features and their relation to prognosis*. Am J Med 1991, 91(6): 612-24.

7. Chiappetta, N., Gruber, B. *The role of mast cells in osteoporosis*. Semin Arthritis Rheum 2006, 36(1): 32-6.

8. Stevens, E.C., Rosenthal, N.S. *Bone marrow mast cell morphologic features and hematopoietic dyspoiesis in systemic mast cell disease*. Am J Clin Pathol 2001, 116(2): 177-82.

9. Pardanani, A., Kimlinger, T., Reeder, T., Li, C.Y., Tefferi, A. *Bone marrow mast cell immunophenotyping in adults with mast cell disease: A prospective study of 33 patients*. Leuk Res 2004, 28(8): 777-83.

10. Worobec, A.S. *Treatment of systemic mast cell disorders*. Hematol Oncol Clin North Am 2000, 14(3): 659-87.

11. Kaplan, A.P. *Clinical practice. Chronic urticaria and angioedema*. N Engl J Med 2002, 346(3): 175-9.

12. Kalivas, J., Breneman, D., Tharp, M., Bruce, S., Bigby, M. *Urticaria: Clinical efficacy of cetirizine in comparison with hydroxyzine and placebo*. J Allergy Clin Immunol 1990, 86(6, Pt. 2): 1014-8.

13. Frieri, M., Alling, D.W., Metcalfe, D.D. *Comparison of the therapeutic efficacy of cromolyn sodium with that of combined chlorpheniramine and cimetidine in systemic mastocytosis. Results of a double-blind clinical trial*. Am J Med 1985, 78(1): 9-14.

14. Friedman, B.S., Metcalfe, D.D. *Effects of tixocortol pivalate on gastrointestinal disease in systemic mastocytosis: A preliminary study*. Clin Exp Allergy 1991, 21(2): 183-8.

15. Carter, M.C., Robyn, J.A., Bressler, P.B., Walker, J.C., Shapiro, G.G., Metcalfe, D.D. *Omalizumab for the treatment of unprovoked anaphylaxis in patients with systemic mastocytosis*. J Allergy Clin Immunol 2007, 119(6): 1550-1.

16. Siebenhaar, F., Kuhn, W., Zuberbier, T., Maurer, M. *Successful treatment of cutaneous mastocytosis and Meniere disease with anti-IgE therapy*. J Allergy Clin Immunol 2007, 120(1): 213-5.

17. Butterfield, J.H. *Response of severe systemic mastocytosis to interferon alpha*. Br J Dermatol 1998, 138(3): 489-95.

18. Casassus, P., Caillat-Vigneron, N., Martin, A. et al. *Treatment of adult systemic mastocytosis with interferon-alpha: Results of a multicentre phase II trial on 20 patients*. Br J Haematol 2002, 119(4): 1090-7.

19. Hauswirth, A.W., Simonitsch-Klupp, I., Uffmann, M. et al. *Response to therapy with interferon alpha-2b and prednisolone in aggressive systemic mastocytosis: Report of five cases and review of the literature.* Leuk Res 2004, 28(3): 249-57.

20. Kluin-Nelemans, H.C., Oldhoff, J.M., Van Doormaal, J.J. et al. *Cladribine therapy for systemic mastocytosis*. Blood 2003, 102(13): 4270-6.

21. Lortholary, O., Vargaftig, J., Feger, F. et al. *Efficacy and safety of cladribine in adult systemic mastocytosis: A French multicenter study of 33 patients.* Blood 2004, 104(11, Pt. 1): Abst 661.

22. Yarden, Y., Kuang, W.J., Yang-Feng, T. et al. *Human proto-oncogene c-kit: A new cell surface receptor tyrosine kinase for an unidentified ligand*. EMBO J 1987, 6(11): 3341-51.

23. Lemmon, M.A., Pinchasi, D., Zhou, M., Lax, I., Schlessinger, J. *Kit receptor dimerization is driven by bivalent binding of stem cell factor*. J Biol Chem 1997, 272(10): 6311-7.

24. Furitsu, T., Tsujimura, T., Tono, T. et al. *Identification of mutations in the coding sequence of the proto-oncogene c-kit in a human mast cell leukemia cell line causing ligand-independent activation of c-kit product*. J Clin Invest 1993, 92(4): 1736-44.

25. Nagata, H., Worobec, A.S., Oh, C.K. et al. *Identification of a point mutation in the catalytic domain of the protooncogene c-kit in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder*. Proc Natl Acad Sci USA 1995, 92(23): 10560-4.

26. Garcia-Montero, A.C., Jara-Acevedo, M., Teodosio, C. et al. *KIT mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: A prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients*. Blood 2006, 108(7): 2366-72.

27. Quintas-Cardama, A., Aribi, A., Cortes, J., Giles, F.J., Kantarjian, H., Verstovsek, S. *Novel approaches in the treatment of systemic mastocytosis*. Cancer 2006, 107(7): 1429-39.

28. Heinrich, M.C., Griffith, D.J., Druker, B.J., Wait, C.L., Ott, K.A., Zigler, A.J. *Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor*. Blood 2000, 96(3): 925-32.

29. Akin, C., Brockow, K., D'Ambrosio, C. et al. *Effects of tyrosine kinase inhibitor STI571 on human mast cells bearing wild-type or mutated c-kit*. Exp Hematol 2003, 31(8): 686-92.

30. Pardanani, A., Elliott, M., Reeder, T. et al. *Imatinib for systemic mast-cell disease*. Lancet 2003, 362(9383): 535-6.

31. Droogendijk, H.J., Kluin-Nelemans. H.J., van Doormaal, J.J., Oranje, A.P., van de Loosdrecht, A.A., van Daele, P.L. *Imatinib mesylate in the treatment of systemic mastocytosis: A phase II trial.* Cancer 2006, 107(2): 345-51.

32. Pardanani, A., Brockman, S.R., Paternoster, S.F. et al. *FIP1L1-PDGFRA fusion: Prevalence and clinicopathologic correlates in 89 consecutive patients with moderate to severe eosinophilia*. Blood 2004, 104(10): 3038-45.

33. Pardanani, A., Ketterling, R.P., Brockman, S.R. et al. *CHIC2 deletion, a surrogate for FIP1L1-PDGFRA fusion, occurs in systemic mastocytosis associated with eosinophilia and predicts response to imatinib mesylate therapy*. Blood 2003, 102(9): 3093-6.

34. Shah, N.P., Lee, F.Y., Luo, R., Jiang, Y., Donker, M., Akin, C. *Dasatinib (BMS-354825) inhibits KITD816V, an imatinib-resistant activating mutation that triggers neoplastic growth in most patients with systemic mastocytosis*. Blood 2006, 108(1): 286-91.

35. Verstovsek, S., Tefferi, A., Cortes, J. et al. *Phase II study of dasatinib (SprycelTM) in Philadelphia chromosome-negative acute and chronic myeloid diseases, including systemic mastocytosis*. Blood [49th Annu Meet Am Soc Hematol (Dec 8-11, Atlanta) 2007] 2007, 110(11): Abst 3551.

36. Growney, J.D., Clark, J.J., Adelsperger, J. et al. *Activation mutations of human c-KIT resistant to imatinib mesylate are sensitive to the tyrosine kinase inhibitor PKC412*. Blood 2005, 106(2): 721-4.

37. Gotlib, J., Berube, C., Growney, J.D. et al. *Activity of the tyrosine kinase inhibitor PKC412 in a patient with mast cell leukemia with the D816V KIT mutation*. Blood 2005, 106(8): 2865-70.

38. Gotlib, J., George, T.I., Corless, C. et al. *The KIT tyrosine kinase inhibitor midostaurine (PKC412) exhibits a high response rate in aggressive systemic mastocytosis (ASM): Interim results of a phase II trial*. Blood [49th Annu Meet Am Soc Hematol (Dec 8-11, Atlanta) 2007] 2007, 110(11): Abst 3536.

39. von Bubnoff, N., Gorantla, S.H., Kancha, R.K., Lordick, F., Peschel, C., Duyster, J. *The systemic mastocytosis-specific activating cKit mutation D816V can be inhibited by the tyrosine kinase inhibitor AMN107*. Leukemia 2005, 19(9): 1670-1.

40. Gleixner, K.V., Mayerhofer, M., Aichberger, K.J. et al. *PKC412 inhibits in vitro growth of neoplastic human mast cells expressing the D816V-mutated variant of KIT: Comparison with AMN107, imatinib, and cladribine (2CdA) and evaluation of cooperative drug effects*. Blood 2006, 107(2): 752-9.

41. Gleixner, K.V., Mayerhofer, M., Sonneck, K. et al. *Synergistic growth-inhibitory effects of two tyrosine kinase inhibitors, dasatinib and PKC412, on neoplastic mast cells expressing the D816V-mutated oncogenic variant of KIT*. Haematologica 2007, 92(11): 1451-9.

42. Verstovsek, S., Akin, C., Francis, G.J. et al. *Effects of AMN107, a novel aminopyrimidine tyrosine kinase inhibitor, on human mast cells bearing wild-type or mutated codon 816 c-kit.* Blood [47th Annu Meet Am Soc Hematol (Dec 10-13, Atlanta) 2005] 2005, 106(11): Abst 3528.

43. Schatz, M., Verhoef, G., Gattermann, N. et al. *A phase II study of AMN107, a novel tyrosine kinase inhibitor, administered to patients (pts) with systemic mastocytosis (SM).* 42nd Annu Meet Am Soc Clin Oncol (ASCO) (June 3-6, Atlanta) 2006, Abst 6588.

44. Quintas-Cardama, A., Kantarjian, H., Verstovsek, S. *Treatment of systemic mastocytosis with denileukin diftitox*. Am J Hematol 2007, 82(12): 1124.