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Diagnosis and classification of mast cell proliferative disorders: Delineation from immunologic diseases and non-mast cell hematopoietic neoplasms

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In mast cell (MC) disorders (mastocytosis), clinical symptoms are caused by the release of chemical mediators from MCs, the pathologic infiltration of neoplastic MCs in tissues, or both. Cutaneous mastocytosis is a benign disease in which MC infiltration is confined to the skin. In pediatric cases cutaneous mastocytosis might regress spontaneously. Systemic mastocytosis (SM) is more frequently diagnosed in adults and is a persistent (clonal) disease of bone marrow—derived myelomastocytic progenitors. The somatic *c-kit* mutation D816V is found in the majority of such patients. The natural clinical course in SM is variable. Whereas most patients remain at the indolent stage for many years, some have aggressive SM (ASM) at diagnosis. Other patients have an associated clonal hematologic non-MC lineage disease (AHNMD). MC leukemia (MCL) is a rare disease variant characterized by circulating MCs and fatal disease progression. The diagnoses of ASM, SM-AHNMD, and MCL might be confused with a variety of endocrinologic, vascular, or immunologic disorders. It is therefore of particular importance to be aware of the possibility of an underlying (malignant) MC disease in patients with unexplained vascular instability, unexplained (anaphylactoid) shock, idiopathic flushing, diarrhea, headache, and other symptoms that might be mediator related. An important diagnostic clue in such cases is an increased serum tryptase

level. The current review provides an overview of mastocytosis and its subvariants and a practical guide that might help to delineate mastocytosis from unrelated systemic disorders. (J Allergy Clin Immunol 2004;114:3-11.)

Key words: Mastocytosis, classification, criteria, c-kit, tryptase

BASIC CONCEPTS IN MAST CELL BIOLOGY

Mast cells (MCs) are metachromatic cells that reside in vascularized tissues and contain chemical pro-inflammatory and vasoactive mediators in cytoplasmic granules.^{1,2} These mediators are released from MCs in response to IgE receptor cross-linking by receptor-bound IgE interacting with specific allergen or by other stimuli.^{1,2} Several mediators, such as MC tryptase, which can be measured in the serum of blood, are surrogate markers that aid in the diagnosis of mastocytosis and represent an indirect parameter (indicator) of the total body number of MCs.³⁻⁵

A number of studies have established that MCs derive from multipotent hematopoietic progenitor cells.⁶⁻¹⁰ These progenitors are detected in the bone marrow, as well as in the peripheral blood.⁶⁻¹² Thus MC precursors are considered to originate in the bone marrow, distribute in the blood, and transmigrate through the endothelial barrier into tissues before undergoing terminal differentiation and maturation.¹⁰ Several cytokines and other factors are considered to contribute to mastopoiesis. A pivotal cytokine in this process is stem cell factor (SCF). SCF induces development of MCs from uncommitted progenitors and promotes terminal differentiation and maturation.⁸⁻¹² The effects of SCF on MCs and their progenitors are mediated through KIT, a transmembrane tyrosine kinase—type receptor encoded by the *c-kit* proto-oncogene.^{10,13} Defects in either the *c-kit* or *SCF* gene in mice result in MC deficiency.^{14,15} All in all, SCF and KIT represent the critical molecules in the regulation

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Abbreviations used

AHNMD: Associated hematologic non—MC lineage disease
 ASM: Aggressive systemic mastocytosis
 CM: Cutaneous mastocytosis
 MC: Mast cell
 MCL: Mast cell leukemia
 SCF: Stem cell factor
 SM: Systemic mastocytosis
 WHO: World Health Organization

of MC development, proliferation, and survival. In line with this concept, gain-of-function mutations in the *c-kit* gene are associated with enhanced growth of MCs.¹⁶⁻²³ It has been documented that such transforming mutations, particularly *c-kit* D816V (Asp-816-Val), are frequently identified in patients with systemic mastocytosis (SM) when the relevant cells and tissues are examined.¹⁷⁻²³

During differentiation from progenitors and in terminal maturation, MCs acquire certain morphologic and phenotypic properties.^{12,24-27} Morphologically, 4 stages of maturation have been described: the nongranulated (tryptase positive) blast cell, the metachromatic blast, the promastocyte (atypical MC type II, MC with bilobed or multilobed nuclei), and the mature MC (typical mononuclear MC).²⁴ Immature MCs (promastocytes and metachromatic blasts) are frequently detected in bone marrow smears of patients with ASM or MCL.²⁴ In patients with indolent SM, the bone marrow smear usually contains MCs that appear more mature. However, in most cases these bone marrow MCs show morphological abnormalities, including (1) prominent cytoplasmic extensions, (2) oval nuclei, and (3) a hypogranulated cytoplasm.²⁴ If at least 2 of these 3 abnormalities are found, bone marrow MCs (on bone marrow smears) are termed atypical MCs type I.²⁴ In some patients with SM, the majority of MCs are round and do not show significant morphologic abnormalities and are thus reminiscent of (normal) tissue MCs. In these cases other minor criteria, apart from atypical morphology of MCs, must be documented to establish the diagnosis of SM. Here one approach is to assess the immunophenotype of MCs. In fact, MCs are known to display a characteristic antigenic phenotype in normal tissues, as well as in SM.²⁵⁻³⁵ In contrast to normal MCs, MCs in SM usually express CD25 and CD2.^{25,29-33,35,36} Immature MCs might express additional antigens. The most immature MC progenitors (both normal and neoplastic) express CD34 and CD13 together with CD117.^{7-10,27}

WORLD HEALTH ORGANIZATION CLASSIFICATION AND DIAGNOSTIC CRITERIA

Mastocytosis is characterized by the abnormal growth, accumulation, or both, of MCs in one or more organ

systems.³⁷⁻⁴¹ Cutaneous mastocytosis (CM) is often diagnosed in childhood but is observed less frequently in adults.⁴¹ By contrast, in adult patients SM is more frequently diagnosed than CM.³⁷⁻⁴¹

In most evaluations the diagnosis of SM is established through an examination of the bone marrow.^{42,43} However, other organs, such as the liver or the gastrointestinal tract, might also be involved.⁴⁴⁻⁴⁸ In contrast to SM, pediatric CM might spontaneously regress in a significant number of cases.^{41,49} Thus in many pediatric patients skin lesions are observed to regress or disappear before or during puberty.^{41,49}

By contrast, SM is considered a persistent clonal disease of myelomastocytic progenitor cells. In most patients with SM, the *c-kit* mutation D816V is detectable.¹⁷⁻²³ Furthermore, in a subgroup of patients with SM (smoldering variant) mutation is not only found in MCs but also in non—MC lineage hematopoietic cells.^{22,23,50-54} On the basis of such findings, SM is recognized by the World Health Organization (WHO) as a separate group of myeloproliferative disorders among hematopoietic neoplasms.^{55,56} This concept is consistent with experimental findings indicating that MCs arise from myelopoietic progenitors⁷⁻¹¹ and with the relatively high incidence of associated hematologic (clonal) non—MC lineage diseases (AHNMD) observed to develop in patients with SM.⁵⁷⁻⁶⁰

On the basis of recent advances in mastocytosis research, an updated consensus classification for mastocytosis was proposed in 2001 and subsequently adopted by the WHO.^{55,61} This updated classification is an extension and refinement of previous classifications,³⁷⁻³⁹ with additional criteria developed during the past few years.⁶² The WHO classification represents an accepted clinical approach that helps in the discrimination between SM and CM, SM and myelomastocytic disorders, and SM and a reactive increase in MCs.^{55,61} Respective criteria to diagnose SM with certainty have been termed SM criteria and are divided into major and minor subsets (Table I). If at least 1 major and 1 minor criterion or at least 3 minor criteria are fulfilled, the diagnosis of SM is established.^{55,61}

The major criterion is the identification of a compact, dense, multifocal MC infiltrate in a bone marrow biopsy section (or other internal organ) that consists of at least 15 coherently aggregating MCs.^{42,43,63} The best available marker for MC detection in such biopsy specimens is tryptase.^{63,64} Notably, antibodies to tryptase detect even small-sized compact or atypical (diffuse or mixed) MC infiltrates.⁶³⁻⁶⁵ Compact MC infiltrates are diagnostic and sometimes are also detected in other internal organs apart from bone marrow.⁴⁴⁻⁴⁸

Minor criteria are important cocriteria confirming the diagnosis of SM. These criteria include the atypical morphology of MCs (spindle-shaped, atypical type I MCs),^{24,62} an atypical phenotype (CD25 and CD2),^{25,31,33,62} increased serum tryptase,^{3,4,62,66} and demonstration of mutations at codon 816 of *c-kit*.^{17-21,62,67} From a practical aspect, the experienced hemato-

TABLE I. WHO criteria for the diagnosis of SM: Criteria

Major*	Multifocal dense infiltrates of MCs in bone marrow or other extracutaneous organs (>15 MCs aggregating)
Minor*	a. MCs in bone marrow or other extracutaneous organs show an abnormal (spindling) morphology (>25%)
	b. Codon 816 <i>c-kit</i> mutation D816V in extracutaneous organs†
	c. MCs in the bone marrow express CD2, CD25, or both
	d. Serum tryptase >20 ng/mL (does not count in patients who have an associated hematopoietic clonal non–MC lineage disease (= AHNMD))

*If at least one major and one minor criterion or 3 minor criteria are fulfilled, the diagnosis of SM can be established.
†Other activating mutations at codon 816 of *c-kit* also count as a minor criterion.

pathologist should be able to diagnose SM on a routinely stained (ie, Giemsa-stained) bone marrow biopsy section in more than 70% of all cases (focal aggregates [major] of spindle-shaped [minor] MCs equals SM). Thus the criteria and classification are straightforward in typical cases of SM. In the absence of spindling and clustering of MCs, however, it is of importance to be sure about the diagnosis of SM and to apply additional disease-related criteria. The application of molecular criteria then becomes crucial for establishing the diagnosis of SM because MCs increase and might even form focal infiltrates in reactive MC hyperplasia or myelo-mastocytic disorders.⁶⁸⁻⁷¹

SM can show either an indolent or aggressive clinical course.^{37-40,72-74} Aggressive systemic mastocytosis (ASM) is characterized by infiltration of multiple organs by MCs, with progressive impairment of organ function evidenced by severe cytopenias, malabsorption, bone fractures, and severe hepatic damage.^{61,73} Respective findings are called C-findings.^{61,73} MC infiltration with organomegaly should not be regarded as a C-finding unless accompanied by evidence of impaired organ function.⁶¹ In fact, organomegaly is also found in patients with an indolent or a smoldering (nonaggressive) course without significant organ dysfunction,⁵⁰⁻⁵⁴ which is regarded as a B-finding.⁶¹ In a subgroup of patients with SM, an AHNMD might be diagnosed.⁵⁷⁻⁶⁰ In these patients WHO criteria for SM, as well as criteria for an AHNMD, are fulfilled.

Mast cell leukemia (MCL) is a rare subentity of SM characterized by a leukemic infiltration of various organs by immature neoplastic MCs.^{30,37-40,61,74} Typically, the bone marrow smear in these patients contains substantial numbers of MCs (≥20%).^{24,40,55,61} In addition, circulating MCs are observed and comprise 10% or more of circulating nucleated cells in typical cases.^{24,40,55,61} The prognosis of patients with MCL is grave.^{24,61,73,74} The most important differential diagnosis to be considered in MCL is myelomastocytic leukemia.^{69,71} Table II shows a summary of variants of mastocytosis recognized by the WHO.

TABLE II. WHO classification of mastocytosis

Variants and subvariants	Abbreviation
Cutaneous mastocytosis	CM
Maculopapular CM*	MPCM
Diffuse CM	DCM
Mastocytoma of skin	
Indolent systemic mastocytosis	ISM
Smoldering SM	SSM
Isolated bone marrow mastocytosis	BMM
Systemic mastocytosis with an associated clonal hematologic non–MC lineage disease	SM-AHNMD†
Aggressive systemic mastocytosis	ASM
With eosinophilia‡	
Mast cell leukemia	MCL
Aleukemic MCL§	
Mast cell sarcoma	MCS
Extracutaneous mastocytoma	

*Also termed urticaria pigmentosa.
†The subtype of the AHNMD has to be defined by WHO criteria as well.
‡In a subgroup of these patients, the *FIPL1-PDGFR*A fusion gene is detectable.
§In these patients circulating MCs are less than 10%.

CLINICAL HALLMARKS AND
PREDIAGNOSTIC CONSIDERATIONS

In most pediatric cases and in the vast majority of adult patients with indolent mastocytosis, skin lesions are the leading clinical finding.^{41,61,75} Biopsy of lesional skin confirms the diagnosis.^{41,61,75} In pediatric patients the disease is usually restricted to the dermis, and a bone marrow examination is not required unless organomegaly or significant peripheral blood abnormalities are present.⁶¹ By contrast, in adult patients, including those in whom mastocytosis was diagnosed before puberty, the diagnostic workup should include a bone marrow study.^{42,43,55,61}

In contrast to indolent SM, patients with aggressive SM or SM-AHNMD often might not exhibit urticaria pigmentosa–like skin lesions. Patients with MCL invariably lack skin lesions.^{37-40,61} This is an important aspect of disease presentation that might be puzzling because many physicians do not consider mastocytosis in the differential diagnosis in patients without typical urticaria pigmentosa–like skin lesions. Such patients are often misdiagnosed with an endocrinologic, immunologic, hematologic, or allergic disorder, especially when organopathy is accompanied by mediator-related symptoms.^{40,76,77} Table III presents a summary of disorders to be considered in the differential diagnosis in patients with aggressive MC disorders with no skin lesions present. In the evaluation of patients with SM, the lack of skin lesions should promote the suspicion of a high-grade MC disorder, although not all subvariants of mastocytosis without skin lesions represent malignant disorders. Thus bone marrow mastocytosis, an MC disease that is considered to be restricted to the bone marrow, is an indolent form of mastocytosis without skin lesions. In these patients the serum tryptase level is relatively low or

TABLE III. SM without skin lesions: Common differential diagnoses

MC disorders	Aggressive SM
	MC leukemia
	SM-AHNMD
	Isolated bone marrow mastocytosis*
Endocrine	Adrenal tumor
	VIPoma
	Gastrinoma
	Carcinoid syndrome
	Diabetes mellitus
	Medullary thyroid carcinoma
	Estrogen-testosterone deficiency
Gastrointestinal	Peptic ulcer disease
	<i>Helicobacter pylori</i> infection
	Ulcerative colitis
	Hepatitis
	Cholecystolithiasis
	Parasitic disease
Cardiovascular	Gluten-sensitive enteropathy
	Allergy
	Idiopathic anaphylaxis
	Cardiac disease, aortic stenosis
	Essential hypertension
Neoplastic/oncologic	Vasculitis
	Malignant lymphoma
	Myeloma
	Histiocytosis
	Bone tumor/metastases
	Hyper eosinophilic syndrome

*In isolated bone marrow mastocytosis, mediator-related symptoms are not recorded as frequently as in other subtypes of mastocytosis.

might even be normal, contrasting with malignant subvariants of SM.⁴

As noted above, a classical clinical hallmark in mastocytosis is the presence of mediator-related symptoms from mild to severe or even life-threatening.⁷⁶⁻⁷⁸ Such mediator-related symptoms might occur in any subvariant of mastocytosis. However, these symptoms per se are not indicative of aggressive disease and thus are not regarded as C-findings.⁷⁶⁻⁷⁸ It is also important to note that such symptoms are often nonspecific and thus confused with other underlying conditions (endocrine, cardiac, pulmonary, allergic, infectious, immunologic, rheumatologic, and gastrointestinal; see Table III). In patients with typical skin lesions, the physician should automatically consider mastocytosis as the correct diagnosis and the major causative factor responsible for clinical symptoms. The same might not be true in evaluating patients without skin lesions—ie, those with aggressive disease variants. Here the physician might not include mastocytosis as a major consideration at first presentation because of the rarity of the disease compared with other differential diagnoses to be considered.

Clinically, an important clue to the involvement of the MC system might be a response to H₁/H₂-antihistamines.^{40,61,72,75-78} However, the symptoms in ASM,

MCL, or SM-AHNMD might be puzzling and might not respond to mediator-targeting drugs in all cases. All in all, it is thus of great importance for the clinician to consider mastocytosis as a potential differential diagnosis in various clinical situations related to mediator effects, even if no skin lesions are found, and then to perform the correct tests.

DIAGNOSTIC EVALUATION AT FIRST PRESENTATION

A first important test to perform in patients with suspected SM is measurement of serum tryptase.^{3-5,61,62,66} In most patients with SM, the serum tryptase concentration is greater than 20 ng/mL.^{3,4,61,66} On the other hand, an increased serum tryptase level is not exclusively found in patients with SM. Patients with myeloid non-MC lineage neoplasms, such as acute or chronic myeloid leukemias, myelodysplastic syndromes, myeloproliferative disorders, or myelomastocytic leukemia, might also have high serum tryptase levels.^{59,66,69,79} Therefore an increased serum tryptase level (as a single parameter) is not diagnostic of SM.⁶¹ Lastly, the serum tryptase level might transiently increase during a severe allergic reaction.^{3,80}

In light of these considerations, the following practical guidelines are proposed in the evaluation of an adult patient without skin lesions but with an increased serum tryptase level (Table IV). In those patients experiencing an unexplained hypotensive (anaphylactoid) event, the tryptase measurement should be repeated a few weeks after the episode. If the serum tryptase level is still increased, a bone marrow examination should be performed (Table IV). In all other patients (ie, without a severe hypotensive episode at the time of serum sampling), the bone marrow should always be examined to diagnose (or exclude) SM or another myeloid (tryptase-positive) neoplasm.

In early childhood the interpretation of the serum tryptase determination might be more difficult than in adults because of a different hypothetic ratio of MC granule volume/whole body volume and of total volume of skin MCs/total body volume. Thus it is not known whether a serum tryptase level somewhat exceeding 20 ng/mL is an indicator for SM in this patient population. Therefore consideration should be given to monitoring the serum tryptase level over time and to not performing a bone marrow puncture unless other signs of a systemic hematologic disease or aggressive subtype of mastocytosis (organomegaly, osteolyses, severe cytopenias, or others) are found (Table IV).

In adults with suspected SM, however, a bone marrow examination should be performed. Such a bone marrow examination includes a thorough examination of histology and of aspirated cells.^{24,42,43,61} The histologic workup should include an appropriate immunohistochemical analysis using antibodies against tryptase, Kit, CD2, and CD25.^{42,43,61-64} Tryptase, largely MC specific, and CD25, only expressed in neoplastic MCs, are of particular

TABLE IV. Practical guide for the diagnostic evaluation of patients with suspected mastocytosis

Initial sign-symptom	Recommended diagnostic procedures
UP-like skin lesions in pediatric cases	1. Skin biopsy (with analysis of <i>c-kit</i> D816V) and serum tryptase*
UP-like skin lesions in adult patients	1. Bone marrow examinations, skin biopsy, and serum tryptase (>20 ng/mL in most SM cases) 2. In case of SM → complete staging: GI tract, x-ray of bones, ultrasound of abdomen, complete blood count, chemistry, coagulation parameters, <i>c-kit</i> mutation status
Mediator-related symptoms but no skin lesions (UP)†	1. Serum tryptase, if >20 ng/mL → 2. 2. Bone marrow examination, if SM → 3. 3. SM—staging†
Severe unexplained allergic or anaphylactoid reaction	1. Serum tryptase, if >20 ng/mL → 2. 2. Repeat serum tryptase a few weeks later: if then, serum tryptase is >20 ng/mL → 3. 3. Bone marrow examination, if SM → 4. 4. SM—staging†

UP, Urticaria pigmentosa.

*Because of a different ratio (ie, MC granule volume/whole body volume in young infants [compared with adults]), a serum tryptase level slightly exceeding 20 ng/mL in these young patients might not be regarded as an indicator for SM. Therefore it is recommended to monitor the serum tryptase level over time but do not perform a bone marrow puncture unless other signs for a systemic hematologic disease are found (organomegaly, osteolyses, severe cytopenias, or others).

†Especially in patients with aggressive MC disorders, skin lesions are absent. Therefore it is of pivotal importance to know the subtype of SM in these patients as soon as possible. In aggressive SM the serum tryptase level is usually higher than in patients with isolated bone marrow mastocytosis (often <20 ng/mL), a benign MC disease in which skin lesions are also absent.

diagnostic value. The aspirated cells should be examined morphologically on bone marrow smears,^{24,61} immunophenotypically by means of flow cytometry with antibodies against CD25 and CD2,^{31,33} and genetically for the presence of codon 816 mutations in *c-kit*.^{17-21,61} The aspirated bone marrow cells should be subjected to a cytogenetic test and a colony-forming assay to determine the numbers of CFU-GM and BFU-E, especially when hematologic abnormalities, such as cytopenias or leukocytosis, are found or when splenomegaly is present.⁶¹ Bone marrow cells should be examined for the presence of BCR/ABL and the *FIPL1-PDGFR*A fusion gene by means of PCR in patients with leukocytosis, eosinophilia, or both.^{61,81}

Rarely, the serum tryptase level might be slightly increased in healthy individuals in whom no mastocytosis

TABLE V. Cyto-reductive therapy in SM

Disease variant	Treatment options
Typical indolent systemic mastocytosis (ISM)	No cyto-reductive treatment required (exception: consider IFN- α 2b for severe osteoporosis, even if no histology documenting ASM is available).
Smoldering systemic mastocytosis (SSM)	Watch and wait in most cases. However, in select cases (eg, progressive organomegaly) IFN- α 2b $\pm$ glucocorticoids can be considered.
SM-AHNMD	Treat AHNMD as if no SM is present and also treat SM as if no AHNMD was found. If splenomegaly and hypersplenism prohibit therapy, consider splenectomy.
Aggressive systemic mastocytosis (ASM)	IFN- α 2b $\pm$ glucocorticoids or cladribine. If splenomegaly and hypersplenism prohibit with slow progression therapy, consider splenectomy.
ASM: rapid progression† and patients who do not respond to IFN- α 2b	Polychemotherapy ($\pm$ IFN- α 2b) or cladribine; bone marrow transplantation for select cases. If splenomegaly and hypersplenism prohibit therapy, consider splenectomy.
ASM without <i>c-kit</i> D816V or with the <i>FIPL1-PDGFR</i> A fusion gene (+ eosinophilia)	Consider STI571 (Imatinib) therapy as an alternative treatment approach.
Mast cell leukemia (MCL)	Polychemotherapy or cladribine ($\pm$ IFN- α 2b). Consider bone marrow transplantation. If splenomegaly and hypersplenism prohibit therapy, consider splenectomy. Consider hydroxyurea as palliative drug.

SM-AHNMD, Systemic mastocytosis with an associated hematologic clonal non-MC lineage disease.

or other hematologic disorder can be detected. It remains unclear whether these individuals have occult mastocytosis or an unrecognized myeloid dysplasia. In regard to the latter possibility, it is noteworthy that some of these individuals exhibit mild cytopenias but no diagnostic dysplasia. In considering occult mastocytosis, it is noteworthy that in very rare patients mastocytosis appears to first become manifest in internal organs other than the bone marrow. One example is splenic mastocytosis.⁸² Another example is MC sarcoma, a malignant MC disease that can develop in various organs and, after a certain latency period, might progress to a clinical picture indistinguishable from that of ASM or MCL.⁸³⁻⁸⁵

NON-MC, TRYPTASE-POSITIVE HEMATOPOIETIC NEOPLASMS AND MYELOMASTOCYTIC DISORDERS (OVERLAP SYNDROMES)

In a subgroup of patients with suspected mastocytosis and increased serum tryptase levels, the final diagnosis will be a hematopoietic (myeloid) neoplasm without frank MC lineage involvement.^{61,66,79} Likewise, about 40% of all patients with acute myeloid leukemia (acute myeloid leukemia without coexisting SM) have an increased serum tryptase level.⁷⁹ An increased serum tryptase level is also found in a subgroup of patients with myelodysplastic and myeloproliferative syndromes, including chronic myeloid leukemia and hypereosinophilic syndrome.^{59,69,86} In most of these patients, no involvement of the MC lineage is found by using morphologic criteria.^{59,69,86} In a few patients with advanced myeloid neoplasms, however, immature metachromatic MCs are observed.^{59,68,69,71} If such cells comprise more than 10% of all nucleated cells in the bone marrow or blood smear but criteria for SM are not fulfilled (no dense MC infiltrates, no CD2 or CD25 on MCs, and no *c-kit* mutations at codon 816), the diagnosis of myelomastocytic leukemia is warranted.^{61,69,71} In other patients, however, criteria for SM might be fulfilled so that the final diagnosis will be SM-AHNMD.⁶¹ In these patients it is of importance to define the nature and subvariant of both the SM and the AHNMD by applying the WHO criteria.^{55,61,69}

THERAPY FOR MASTOCYTOSIS

Because no curative therapies for mastocytosis are available at present, mastocytosis should be treated according to the symptoms recorded in each patient.^{40,72,73,76,78} In patients with mediator-related symptoms, mediator-targeting drugs are prescribed.^{40,72,76,78} In addition, these patients should avoid triggering stimuli that might cause mediator release from MCs.⁷⁶ In patients with a history of episodes of hypotension (anaphylactoid shock), self-administration of epinephrine on demand by using an Epi-Pen or similar approach has been recommended.^{40,76,78} Some authors have recommended the use of cytoreductive or growth-inhibitory drugs for these patients.^{76,87} However, such therapeutic maneuvers and their potential beneficial effects have to be balanced against the long-term risk of the use of in part mutagenic drugs and the long-term side effects of these therapies.⁷³

In patients with SM-AHNMD, separate treatment plans for the SM and AHNMD components of the disease should be established. The general recommendation for these patients is to treat the SM as if there was no AHNMD and the AHNMD as if there was no SM.^{40,56,59,76,78}

In patients experiencing an aggressive growth of MCs, cytoreductive drugs might be recommended and used together with anti-mediator-type drugs (Table V).^{61,73,76,78} The best-studied drug is IFN- α , with or without a glucocorticoid. IFN- α is considered to affect the

growth of early myeloid progenitor cells and to produce a major clinical response in about 15% to 20% of all patients with ASM.⁸⁸⁻⁹³ Another promising drug is cladribine. Cladribine reportedly reduces the MC burden in patients with ASM.⁹⁴⁻⁹⁷ However, not all patients with ASM will respond to cladribine (unpublished data). More recently, the use of targeted drugs in the treatment of patients with aggressive subtypes of SM has been proposed. When considering the use of such drugs like Imatinib (STI571), it is of importance to define the exact molecular defects that underly mastocytosis and the potential targets expressed in neoplastic cells.^{97,98} Thus whereas several targets and altered genes (eg, wild-type *c-kit*, *c-kit* Phe522Cys, or the *FIPL1-PDGFR* fusion gene) are associated with a response to Imatinib, other gene defects, such as the *c-kit* mutation Asp816Val = D816V, are associated with resistance to Imatinib.⁹⁸⁻¹⁰¹ The major problem in this regard is that most patients with SM exhibit *c-kit* D816V,¹⁰² so that Imatinib is not expected to be used widely to treat SM. All in all, the ideal drug (combination) to be used in patients with ASM and MCL has not yet been reported.

SUMMARY AND FUTURE DIRECTIONS

Mastocytosis is a term collectively used for a heterogeneous group of disorders of myelomastocytic progenitor cells. During the past few years, much has been learned about neoplastic MCs and disease variants. Thus by using defined criteria, it is now possible to discriminate between MC disorders and other systemic diseases with reasonable certainty, even if mastocytosis shows an atypical presentation. In addition, much is now understood about disease-specific gene defects occurring in patients with mastocytosis and related disorders. Some of the altered genes and molecules have now been identified as potential targets of drug therapy. These developments lead to the expectation of improved therapy of mastocytosis in the foreseeable future.

REFERENCES

- Schwartz LB. Mast cells and basophils. In: Schwartz LB, Zweiman B, editors. Inflammatory mechanisms of allergic diseases. New York: Marcel Dekker; 2002. p. 3-42.
- Valent P, Sillaber C, Bettelheim P. The growth and differentiation of mast cells. *Prog Growth Factor Res* 1991;3:27-41.
- Schwartz LB, Sakai K, Bradford TR, Ren S, Zweiman B, Worobec AS, et al. The alpha form of human tryptase is the predominant type present in blood at baseline in normal subjects and is elevated in those with systemic mastocytosis. *J Clin Invest* 1995;96:2702-10.
- Sperr WR, Jordan JH, Fiegl M, Escribano L, Dirnhofer S, Semper H, et al. Serum tryptase levels in patients with mastocytosis: correlation with mast cell burden and implication for defining the category of disease. *Int Arch Allergy Immunol* 2002;128:136-41.
- Akin C, Metcalfe DD. Surrogate markers of disease in mastocytosis. *Int Arch Allergy Immunol* 2002;127:133-6.
- Kirshenbaum AS, Goff JP, Kessler SW, Mican JM, Zsebo KM, Metcalfe DD. Effects of IL-3 and stem cell factor on the appearance of human basophils and mast cells from CD34+ pluripotent progenitor cells. *J Immunol* 1992;148:772-7.

7. Kirshenbaum AS, Goff JP, Semere T, Foster B, Scott LM, Metcalfe DD. Demonstration that human mast cells arise from a progenitor cell population that is CD34+, c-kit+, and expresses aminopeptidase N (CD13). *Blood* 1999;94:2333-42.
8. Agis H, Willheim M, Sperr WR, Wilfling A, Krömer E, Kabrna E, et al. Monocytes do not make mast cells when cultured in the presence of SCF. Characterization of the circulating mast cell progenitor as a c-kit+, CD34+, Ly-, CD14-, CD17-, colony forming cell. *J Immunol* 1993;151:4221-7.
9. Rottem M, Okada T, Goff JP, Metcalfe DD. Mast cells cultured from peripheral blood of normal donors and patients with mastocytosis originate from a CD34+/FceRI- cell population. *Blood* 1994;84:2489-96.
10. Valent P. The riddle of the mast cell: c-kit ligand as missing link? *Immunol Today* 1994;15:111-4.
11. Mitsui H, Furitsu T, Dvorak AM, Irani AM, Schwartz LB, Inagaki N, et al. Development of human mast cells from umbilical cord blood cells by recombinant human and murine c-kit ligand. *Proc Natl Acad Sci U S A* 1990;90:735-9.
12. Valent P, Spanblöchl E, Sperr WR, Sillaber Ch, Agis H, Zsebo K, et al. Induction of differentiation of human mast cells from bone marrow and peripheral blood mononuclear cells by recombinant human stem cell factor (SCF)/kit ligand (KL) in long term culture. *Blood* 1992;80:2237-45.
13. Sillaber C, Strobl H, Bevec D, Ashman LK, Butterfield JH, Lechner K, et al. IL-4 regulates c-kit proto-oncogene product expression in human mast and myeloid progenitor cells. *J Immunol* 1991;147:4224-8.
14. Kitamura Y, Go S, Hatanaka S. Decrease of mast cells in W/Wv mice and their increase by bone marrow transplantation. *Blood* 1978;52:447-52.
15. Kitamura Y, Go S. Decreased production of mast cells in Sl/Sl mice. *Blood* 1979;53:492-7.
16. Furitsu T, Tsujimura T, Tono T, Ikeda H, Kitayama H, Koshimizu U, 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 the c-kit product. *J Clin Invest* 1993;92:1736-44.
17. Feger F, Ribadeau Dumas A, Leriche L, Valent P, Arock M. Kit and c-kit mutations in mastocytosis: a short overview with special reference to novel molecular and diagnostic concepts. *Int Arch Allergy Immunol* 2002;127:110-4.
18. Nagata H, Worobec AS, Oh CK, Chowdhury BA, Tannenbaum S, Suzuki Y, 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 U S A* 1995;92:10560-4.
19. Longley BJ, Tyrrell L, Lu SZ, Ma YS, Langley K, Ding TG, et al. Somatic c-kit activating mutation in urticaria pigmentosa and aggressive mastocytosis: establishment of clonality in a human mast cell neoplasm. *Nat Genet* 1996;12:312-4.
20. Longley BJ, Metcalfe DD, Tharp M, Wang X, Tyrrell L, Lu S-Z, et al. Activating and dominant inactivating c-kit catalytic domain mutations in distinct forms of human mastocytosis. *Proc Natl Acad Sci U S A* 1999;96:1609-14.
21. Buttner C, Henz BM, Welker P, Sepp NT, Grabbe J. Identification of activating c-kit mutations in adult-, but not childhood-onset indolent mastocytosis: a possible explanation for divergent clinical behaviour. *J Invest Dermatol* 1998;111:1227-31.
22. Akin C, Kirschenbaum AS, Semere T, Worobec AS, Scott LM, Metcalfe DD. Analysis of the surface expression of c-kit and occurrence of the c-kit Asp816Val activating mutation in T cells, B cells, and myelomonocytic cells in patients with mastocytosis. *Exp Hematol* 2000;28:140-7.
23. Yavuz AS, Lipsky PE, Yavuz S, Metcalfe DD, Akin C. Evidence for the involvement of a hematopoietic progenitor cell in systemic mastocytosis from single cell analysis of mutations in the c-kit gene. *Blood* 2002;100:661-5.
24. Sperr WR, Escribano L, Jordan JH, Scherthaner GH, Kundi M, Horny H-P, et al. Morphologic properties of neoplastic mast cells: delineation of stages of maturation and implication for cytological grading of mastocytosis. *Leuk Res* 2001;25:529-36.
25. Valent P, Scherthaner GH, Sperr WR, Fritsch G, Agis H, Willheim M, et al. Variable expression of activation-linked surface antigens on human mast cells in health and disease. *Immunol Rev* 2001;179:74-81.
26. Xia HZ, Du Z, Craig S, Klisch G, Noben-Trauth N, Kochan JP, et al. Effect of recombinant human IL-4 on tryptase, chymase, and Fc epsilon receptor type I expression in recombinant human stem cell factor-dependent fetal liver-derived human mast cells. *J Immunol* 1997;159:2911-21.
27. Shimizu Y, Sakai K, Miura T, Narita T, Tsukagoshi H, Satoh Y, et al. Characterization of adult-type mast cells derived from human bone marrow CD34+ cells cultured in the presence of stem cell factor and interleukin-6. Interleukin-4 is not required for constitutive expression of CD54, Fc epsilon RI alpha and chymase, and CD13 expression is reduced during differentiation. *Clin Exp Allergy* 2002;32:872-80.
28. Valent P, Ashman LK, Hinterberger W, Eckersberger F, Majdic O, Lechner K, et al. Mast cell typing: demonstration of a distinct hemopoietic cell type and evidence for immunophenotypic relationship to mononuclear phagocytes. *Blood* 1989;73:1778-85.
29. Valent P, Bettelheim P. Cell surface structures on human basophils and mast cells: biochemical and functional characterization. *Adv Immunol* 1992;52:333-423.
30. Dalton R, Chan L, Batten E, Eridani S. Mast cell leukemia: evidence for bone marrow origin of the pathological clone. *Br J Haematol* 1986;64:397-406.
31. Escribano L, Orfao A, Diaz-Agustin B, Villarrubia J, Cervero C, Lopez A, et al. Indolent systemic mast cell disease in adults: immunophenotypic characterization of bone marrow mast cells and its diagnostic implication. *Blood* 1998;91:2731-6.
32. Scherthaner GH, Jordan JH, Ghannadan M, Agis H, Bevec D, Nuñez R, et al. Expression, epitope analysis, and functional role of the LFA-2 antigen detectable on neoplastic mast cells. *Blood* 2001;98:3784-92.
33. Escribano L, Díaz-Agustín B, Bellas C, Navalón R, Nuñez R, Sperr WR, et al. Utility of flow cytometric analysis of mast cells in the diagnosis and classification of adult mastocytosis. *Leuk Res* 2001;25:563-70.
34. Ghannadan M, Hauswirth A, Scherthaner G-H, Müller MR, Klepetko W, Schatzl G, et al. Detection of novel CD antigens on the surface of human mast cells and basophils. *Int Arch Allergy Immunol* 2002;127:299-307.
35. Jordan H, Walchshofer S, Jurecka W, Mosberger I, Sperr WR, Wolff K, et al. Immunohistochemical properties of bone marrow mast cells in systemic mastocytosis: evidence for expression of CD2, CD117/Kit, and bcl-xL. *Hum Pathol* 2001;32:545-52.
36. Horny HP, Lange K, Sotlar K, Valent P. Increase of bone marrow lymphocytes in systemic mastocytosis: reactive lymphocytosis or malignant lymphoma? Immuno-histochemical and molecular findings on routinely processed bone marrow biopsy specimens. *J Clin Pathol* 2003;56:575-8.
37. Parwaresch MR, Horny H-P, Lennert K. Tissue mast cells in health and disease. *Path Res Pract* 1985;179:439-61.
38. Metcalfe DD. Classification and diagnosis of mastocytosis: current status. *J Invest Dermatol* 1991;96:2S-4S.
39. Valent P. Biology, classification and treatment of human mastocytosis. *Wien Klin Wochenschr* 1996;108:385-97.
40. Valent P, Akin C, Sperr WR, Horny HP, Arock M, Lechner K, et al. Diagnosis and treatment of systemic mastocytosis: state of the art. *Br J Haematol* 2003;122:1-23.
41. Wolff K, Komar M, Petzelbauer P. Clinical and histopathological aspects of cutaneous mastocytosis. *Leuk Res* 2001;25:519-28.
42. Horny H-P, Valent P. Diagnosis of mastocytosis: General histopathological aspects, morphological criteria, and immunohistochemical findings. *Leuk Res* 2001;25:543-51.
43. Horny HP, Valent P. Histopathological and immunophenotypical aspects of mastocytosis. *Int Arch Allergy Immunol* 2002;127:115-7.
44. Horny H-P, Ruck M, Kaiserling E. Spleen findings in generalized mastocytosis. A clinicopathologic study. *Cancer* 1992;70:459-68.
45. Horny H-P, Kaiserling E, Parwaresch MR, Lennert K. Lymph node findings in generalized mastocytosis. *Histopathology* 1992;21:439-46.
46. Horny H-P, Kaiserling E, Campbell M, Parwaresch MR, Lennert K. Liver findings in generalized mastocytosis. A clinicopathologic study. *Cancer* 1989;63:532-8.

47. Metcalfe DD. The liver, spleen, and lymph nodes in mastocytosis. *J Invest Dermatol* 1991;96:45S-46S.
48. Travis WD, Li CY. Pathology of the lymph node and spleen in systemic mast cell disease. *Mod Pathol* 1988;1:4-14.
49. Caplan RM. The natural course of urticaria pigmentosa. *Arch Dermatol* 1963;87:146-57.
50. Akin C, Scott LM, Metcalfe DD. Slowly progressing mastocytosis with high mast cell burden and no evidence of a non-mast cell hematologic disorder: an example of a smoldering case? *Leuk Res* 2001;25:635-8.
51. Jordan JH, Fritsche-Polanz R, Sperr WR, Mitterbauer G, Födinger M, Schernthaner GH, et al. A case of smouldering mastocytosis with high mast cell burden, monoclonal myeloid cells, and C-KIT mutation Asp-816-Val. *Leuk Res* 2001;25:627-34.
52. Hauswirth A, Sperr WR, Ghannadan M, Schernthaner G-H, Jordan JH, Fritsche-Polanz R, et al. A case of smouldering mastocytosis with peripheral blood eosinophilia and lymphadenopathy. *Leuk Res* 2002;26:601-6.
53. Sotlar K, Marafioti T, Griesser H, Theil J, Aepinus C, Jaussi R, et al. Detection of c-kit mutation Asp-816-Val in microdissected bone marrow infiltrates in a case of systemic mastocytosis associated with chronic myelomonocytic leukemia. *Mol Pathol* 2000;53:188-93.
54. Valent P, Akin C, Sperr WR, Horny H-P, Metcalfe DD. Smouldering mastocytosis: a new type of systemic mastocytosis with slow progression. *Int Arch Allergy Immunol* 2002;127:137-9.
55. Valent P, Horny H-P, Li CY, Longley JB, Metcalfe DD, Parwaresch RM, et al. Mastocytosis (mast cell disease). World Health Organization (WHO) classification of tumours. Pathology and genetics. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. *Tumours of haematopoietic and lymphoid tissues*. Vol 1. World Health Organization. Lyon, France: IARC Press; 2001. p. 291-302.
56. Valent P, Akin C, Sperr WR, Horny H-P, Metcalfe DD. Mast cell proliferative disorders: current view on variants recognized by the World Health Organization. *Hematol Oncol Clin North Am* 2003;17:1227-41.
57. Horny H-P, Ruck M, Wehrmann M, Kaiserling E. Blood findings in generalized mastocytosis: evidence of frequent simultaneous occurrence of myeloproliferative disorders. *Br J Haematol* 1990;76:186-93.
58. Lawrence JB, Friedman BS, Travis WD, Chinchilli VM, Metcalfe DD, Gralnick HR. Hematologic manifestation of systemic mast cell disease: a prospective study of laboratory and morphologic features and their relation to prognosis. *Am J Med* 1991;91:612-24.
59. Sperr WR, Horny H-P, Lechner K, Valent P. Clinical and biologic diversity of leukemias occurring in patients with mastocytosis. *Leuk Lymphoma* 2000;37:473-86.
60. Travis WD, Li CY, Yam LT, Bergstralh EJ, Sweet RG. Significance of systemic mast cell disease with associated hematologic disorders. *Cancer* 1988;62:965-72.
61. Valent P, Horny H-P, Escubano L, Longley JB, Li CY, Schwartz LB, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. Conference Report of Year 2000 Working Conference on Mastocytosis. *Leuk Res* 2001;25:603-25.
62. Valent P, Escubano L, Parwaresch MR, Schemmel V, Schwartz LB, Sotlar K, et al. Recent advances in mastocytosis research. *Int Arch Allergy Immunol* 1999;120:1-7.
63. Horny H-P, Sillaber C, Menke D, Kaiserling E, Wehrmann M, Stehberger B, et al. Diagnostic utility of staining for tryptase in patients with mastocytosis. *Am J Surg Pathol* 1998;22:1132-40.
64. Li WV, Kapadia SB, Sonmez-Alpan E, Swerdlow SH. Immunohistochemical characterization of mast cell disease in paraffin sections using tryptase, CD68, myeloperoxidase, lysozym, and CD20 antibodies. *Mod Pathol* 1996;9:982-8.
65. Li C-Y. Diagnosis of mastocytosis: value of cytochemistry and immunohistochemistry. *Leuk Res* 2001;25:537-41.
66. Schwartz LB. Clinical utility of tryptase levels in systemic mastocytosis and associated hematologic disorders. *Leuk Res* 2001;25:553-62.
67. Longley BJ, Reguera MJ, Ma Y. Classes of c-KIT activating mutations: proposed mechanisms of action and implications for disease classification and therapy. *Leuk Res* 2001;25:571-6.
68. Prokocimer M, Polliack A. Increased bone marrow mast cells in preleukemic syndromes, acute leukemia, and lymphoproliferative disorders. *Am J Clin Pathol* 1981;75:34-8.
69. Valent P, Sperr WR, Samorapoompichit P, Geissler K, Lechner K, Horny HP, et al. Myelomastocytic overlap syndromes: biology, criteria, and relationship to mastocytosis. *Leuk Res* 2001;25:595-602.
70. Jordan JH, Sperr WR, Lechner K, Schernthaner G-H, Fritsche-Polanz R, et al. Stem cell factor-induced bone marrow mast cell hyperplasia mimicking systemic mastocytosis (SM): histopathologic and morphologic evaluation with special reference to novel SM-criteria. *Leuk Lymphoma* 2002;43:575-82.
71. Valent P, Samorapoompichit P, Sperr WR, Horny H-P, Lechner K. Myelomastocytic leukemia: myeloid neoplasm characterized by partial differentiation of mast cell-lineage cells. *Hematol J* 2002;3:90-4.
72. Austen KF. Systemic mastocytosis. *N Engl J Med* 1992;326:639-40.
73. Valent P, Akin C, Sperr WR, Escubano L, Arock M, Horny HP, et al. Aggressive systemic mastocytosis and related mast cell disorders: current treatment options and proposed response criteria. *Leuk Res* 2003;27:635-41.
74. Travis WD, Li CY, Hogaland HC, Travis LB, Banks PM. Mast cell leukemia: report of a case and review of the literature. *Mayo Clin Proc* 1986;61:957-66.
75. Hartmann K, Henz BM. Cutaneous mastocytosis—clinical heterogeneity. *Int Arch Allergy Immunol* 2002;127:143-6.
76. Escubano L, Akin C, Castells M, Orfao A, Metcalfe DD. Mastocytosis: current concepts in diagnosis and treatment. *Ann Hematol* 2002;81:677-90.
77. Castells M, Austen KF. Mastocytosis: mediator-related signs and symptoms. *Int Arch Allergy Immunol* 2002;127:147-52.
78. Worobec AS. Treatment of systemic mast cell disorders. *Hematol Oncol North Am* 2000;14:659-87.
79. Sperr WR, Jordan JH, Baghestanian M, Kiener H, Samorapoompichit P, Semper H, et al. Expression of mast cell tryptase by myeloblasts in a group of patients with acute myeloid leukemia. *Blood* 2001;98:2200-9.
80. Schwartz LB, Metcalfe DD, Miller JS, Earl H, Sullivan T. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. *N Engl J Med* 1987;316:1622-6.
81. Tefferi A, Pardanani A. Clinical, genetic, and therapeutic insights into systemic mast cell disease. *Curr Opin Hematol* 2004;11:58-64.
82. Wimazal F, Schwarzmeier J, Sotlar K, Simonitsch I, Sperr WR, Fritsche-Polanz R, et al. Splenic mastocytosis: report of two cases and detection of the transforming c-kit mutation D816V. *Leuk Lymphoma*. In press.
83. Horny H-P, Parwaresch MR, Kaiserling E, Muller K, Olbermann M, Mainzer K, et al. Mast cell sarcoma of the larynx. *J Clin Pathol* 1986;39:596-602.
84. Kojima M, Nakamura S, Itoh H, Ohno Y, Masawa N, Joshita T, et al. Mast cell sarcoma with tissue eosinophilia arising in the ascending colon. *Mod Pathol* 1999;12:739-43.
85. Guenther PP, Huebner A, Sobottka SB, Neumeister V, Weissbach G, Todt H, et al. Temporary response of localized intracranial mast cell sarcoma to combination chemotherapy. *J Pediatr Hematol Oncol* 2001;23:134-8.
86. Sperr WR, Stehberger B, Wimazal F, Baghestanian M, Schwartz LB, Kundi M, et al. Serum tryptase measurements in patients with myelodysplastic syndromes. *Leuk Lymphoma* 2002;43:1097-105.
87. Casasus P, Caillat-Vigneron N, Martin A, Simon J, Gallais V, Beaudry P, et al. Treatment of adult systemic mastocytosis with interferon-alpha: results of a multicentre phase II trial on 20 patients. *Br J Haematol* 2002;119:1090-7.
88. Kluin-Nelemans HC, Jansen JH, Breukelman H, Wolthers BG, Kluin PM, et al. Response to interferon alfa-2b in a patient with systemic mastocytosis. *N Engl J Med* 1992;326:619-23.
89. Delaporte E, Pierard E, Wolters BG, Desreumaux P, Janin A, Cortot A, et al. Interferon-alpha in combination with corticosteroids improves systemic mast cell disease. *Br J Dermatol* 1995;132:479-82.
90. Worobec AS, Kirshenbaum AS, Schwartz LB, Metcalfe DD. Treatment of three patients with systemic mastocytosis with interferon alpha-2b. *Leuk Lymphoma* 1996;22:501-8.

91. Weide R, Ehlenz K, Lorenz W, Walthers E, Klausmann M, Pfluger KH. Successful treatment of osteoporosis in systemic mastocytosis with interferon alpha-2b. *Ann Hematol* 1996;72:41-3.
92. Butterfield JH. Response of severe systemic mastocytosis to interferon alpha. *Br J Dermatol* 1998;138:489-95.
93. Hauswirth AW, Simonitsch-Klupp I, Uffmann M, Koller E, Sperr WR, Lechner K, 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;28:249-57.
94. Tefferi A, Li CY, Butterfield JH, Hoagland HC. Treatment of systemic mast-cell disease with cladribine. *N Engl J Med* 2001;344:307-9.
95. Kluin-Nelemans HC, Oldhoff JM, Van Doormaal JJ, Van't Wout JW, Verhoef G, Gerrits WB, et al. Cladribine therapy for systemic mastocytosis. *Blood* 2003;102:4270-6.
96. Escribano L, Perez de Oteyza J, Nunez R, Orfao A. Cladribine induces immunophenotypical changes in bone marrow mast cells from mastocytosis. Report of a case of mastocytosis associated with a lymphoplasmacytic lymphoma. *Leuk Res* 2002;26:1043-6.
97. Tefferi A. Treatment of systemic mast cell disease: beyond interferon. *Leuk Res* 2004;28:223-4.
98. Akin C, Brockow K, D'Ambrosio C, Kirshenbaum AS, Ma Y, Longley BJ, et al. Effects of tyrosine kinase inhibitor STI571 on human mast cells bearing wild-type or mutated c-kit. *Exp Hematol* 2003;31:686-92.
99. Akin C, Fumo G, Yavuz AS, Lipsky PE, Neckers L, Metcalfe DD. A novel form of mastocytosis associated with a transmembrane c-Kit mutation and response to imatinib. *Blood*. In press 2003.
100. Zermati Y, De Sepulveda P, Feger F, Letard S, Kersual J, Casteran N, et al. Effect of tyrosine kinase inhibitor STI571 on the kinase activity of wild-type and various mutated c-kit receptors found in mast cell neoplasms. *Oncogene* 2003;22:660-4.
101. Pardanani A, Ketterling RP, Brockman SR, Flynn HC, Paternoster SF, Shearer BM, et al. CHIC2 deletion, a surrogate for FIP1L1-PDGFRFA fusion, occurs in systemic mastocytosis associated with eosinophilia and predicts response to imatinib mesylate therapy. *Blood* 2003;102:3093-6.
102. Fritsche-Polanz R, Jordan JH, Feix A, Sperr WR, Sunder-Plassmann G, Valent P, et al. Mutation analysis of C-KIT in patients with myelodysplastic syndromes without mastocytosis and cases of systemic mastocytosis. *Br J Haematol* 2001;113:357-64.