Kit Mutations

New Insights and Diagnostic Value

Lorenzo Falchi, MD[a], Srdan Verstovsek, MD, PhD[b,*]

KEYWORDS

• KIT mutations • *KIT* D816V • Cutaneous mastocytosis • Systemic mastocytosis • Imatinib • Midostaurin • Avapritinib

KEY POINTS

- KIT mutations are the molecular hallmark of mastocytosis and are present in the vast majority of patients, despite the clinical heterogeneity of the disease.
- *KIT* D816V is the most common KIT mutation, particularly in patients with more advanced forms, and it is believed to represent a driver lesion of the disease.
- Testing for *KIT* D816V is part of the diagnostic criteria for mastocytosis. The mutation can be detected through allele-specific–oligonucleotide quantitative polymerase chain reaction in peripheral blood in most patients.
- Mutated KIT inhibition with imatinib mesylate has represented the first advancement in the targeted therapy of systemic mastocytosis, but it is ineffective in patients with *KIT* D816V.
- Novel agents capable of overcoming *KIT* D816V–mediated tyrosine kinase inhibitor resistance include the multikinase inhibitor midostaurin, the selective *KIT* D816V inhibitor avapritinib, and the so-called switch-pocket inhibitors.

INTRODUCTION

Mastocytosis is a neoplastic disorder originating from the malignant transformation and clonal proliferation of mast cells (MCs), which accumulate in one or multiple organs. The true incidence of the disease is difficult to ascertain due to potential underdiagnosis. It is estimated, however, at 0.89 per 100,000 per year, according to a recent European study.[1] The prevalence of mastocytosis was hypothesized to be approximately 1 in 10,000 people.[2]

The clinical spectrum of mastocytosis ranges from isolated cutaneous forms (cutaneous mastocytosis [CM]) that is more frequent in younger patients, with tendency to

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[a] Division of Hematology/Oncology, Columbia University Medical Center, 177 Fort Washington Avenue, MHB 6GN-435, New York, NY 10032, USA; [b] Leukemia Department, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 428, Houston, TX 77030, USA

* Corresponding author.

E-mail address: sverstov@mdanderson.org

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spontaneously resolve,[3] to aggressive diffuse variants (systemic mastocytosis [SM]) typically seen in adult patients and associated with poorer outcome.[4] In addition, because SM is a hematopoietic stem cell disorder, it can coexist with other World Health Organization (WHO)-defined myeloid (or, more rarely, lymphoid) neoplasms.[5]

Once comprised within the group of myeloproliferative neoplasms (MPNs), mastocytosis is now recognized as a distinct clinicopathologic entity in the 2016 revision of the WHO classification of myeloid tumors (**Box 1**).[6]

The symptoms of mastocytosis are largely due to the release of MC products. Histamine (acting through receptors H_1–H_4) mediates vasodilation, brochoconstriction, gastrointestinal hypermotility, and increased gastric acid production, which account for rapid-onset symptoms like headache, hypotension, pruritus, urticaria, angioedema, cramping, diarrhea, and anaphylaxis.[7] Chymase is responsible for cardiovascular symptoms like arrhythmias, myocardial ischemia, and hypotension. Other mediators of mastocytosis symptoms include platelet-activating factor, prostaglandin D2,[8] serotonin, and substance P.[9] Rare manifestations of mastocytosis include tissue eosinophilia (due to interleukin [IL]-5 production) and bone remodeling (due to space-occupying MC burden, as well as to IL-1β and IL-6 secreted by MCs).[10]

CM, the most common form of mastocytosis, can present as urticaria pigmentosa, particularly on the torso and extremities; diffuse CM; or solitary skin mastocytoma. SM is defined by MC involvement of end organs other than the skin (most commonly the bone marrow [BM]). Indolent SM primarily causes gastrointestinal, skin, and cognitive symptoms, but does not affect organ function (e.g., BM, although involved with mastocytosis, functions well and patients have normal blood cell counts). Smoldering SM is a subtype of indolent SM, with organ enlargement (B findings) but preserved organ function, and possibly with more variable course.[11] Although indolent SM is a rather benign condition, end-organ damage is the

Box 1
World Health Organization classification of mastocytosis (2016)

1. Cutaneous mastocytosis
   a. Urticaria pigmentosa/maculopapular cutaneous mastocytosis
   b. Diffuse cutaneous mastocytosis
   c. Solitary mastocytoma of skin
2. SM
   a. ISM: meets criteria for SM; no C findings; no evidence of associated clonal hematologic non–MC lineage disease[a]
   b. Smoldering SM: as above (ISM) but with 2 or more B findings and no C findings[a]
   c. SM-AHN[b]: meets criteria for SM and criteria for an associated hematologic neoplasm as a distinct entity per the WHO classification
   d. ASM: meets criteria for SM; 1 or more C findings; no evidence of MCL[a]
   e. MCL
3. MC sarcoma
   a. Unifocal MC tumor; no evidence of SM; destructive growth pattern; high-grade cytology

[a] These subtypes require information regarding B findings and C findings for complete diagnosis (see **Box 2**), all of which may not be available at the time of initial tissue diagnosis.

[b] The terms, systemic mastocytosis with an associated clonal hematologic non-MC lineage disease (SM-AHNMD) and SM-AHN, can be used synonymously.

Adapted from Swerdlow SH, Campo E, Harris N, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th edition. Lyon (France): International Agency for Research on Cancer (IARC); 2017; with permission.