How we diagnose and treat WHO-defined systemic mastocytosis in adults

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Current classification and diagnosis of systemic mastocytosis, and its distinction from other myeloid malignancies associated with bone marrow mastocytosis, remain challenging for both clinicians and hematopathologists. In its upcoming revision, due out in 2008, the World Health Organization (WHO) classification system for myeloid malignancies considers mast cell disease as a myeloproliferative neoplasm and systemic mastocytosis as a subcategory of mast cell disease with bone marrow involvement.[1] At the same time, the WHO document distinguishes the usually *KIT*-mutated systemic mastocytosis from myeloid neoplasms associated with bone marrow mastocytosis and *PDGFR* mutations (e.g. *FIP1L1-PDGFRA, PRKG2-PDGFRB*).[2-6] The latter are often associated with eosinophilia or basophilia and sensitive to treatment with imatinib. WHO-defined systemic mastocytosis is sometimes associated with a clonally-related second myeloid neoplasm,[7-11] which is not surprising considering its origin as a stem cell disease with multilineage clonal involvement.[12-16] Conversely, an otherwise well-defined myeloid malignancy, such as myelodysplastic syndrome or a non-mast cell disease myeloproliferative neoplasm, might harbor neoplastic mast cells.[17]

Our approach to diagnosis in systemic mastocytosis starts with bone marrow examination with tryptase staining and mast cell CD25 immunophenotyping. The former enhances morphologic and the latter immunophenotypic distinction between normal (round and CD25-negative)

and abnormal (spindle-shaped and CD25-positive) mast cells.[18,19] Bone marrow examination also allows detection of a second hematologic neoplasm, if present.[7,9] In addition, in the presence of blood eosinophilia, we screen for *FIP1L1-PDGFRA*, using either FISH or RT-PCR.[20] By contrast, we rely on conventional cytogenetics to identify cases of bone marrowmastocytosis associated with a *PDGFRB* rearrangement (i.e. chromosomal translocations involving 5q31-32).[6] In general, we consider mutation screening for *KIT*D816V and measurement of serum tryptase or urinary histamine metabolites as being complementary for the diagnosis of mast cell disease.[21-23] It is to be noted that the likelihood of detecting a KIT mutation is significantly higher with the use of both highly sensitive PCR-based assay and mast cell-enriched test samples.[24,25]

After establishing the presence of abnormal bone marrow mast cells, we strictly follow the revised WHO criteria in assigning the specific diagnosis of *myeloid neoplasm associated with PDGFR rearrangement*, in the presence of either a *PDGFRA* or *PDGFRB* mutation.[1] In all other instances, we use the term *systemic mastocytosis*, provided bone marrow mastocytosis is the prominent feature in terms of both bone marrow histology and clinical presentation. Drug therapy has not been shown to favorably affect survival in systemic mastocytosis and the experience with allogeneic stem cell transplantation has been too limited to allow discussion.[26] Therefore, current therapy in WHO-defined systemic mastocytosis is palliative and directed at mast cell degranulation symptoms (e.g. pruritus, urticaria, angioedema, flushing, nausea, vomiting, abdominal pain, diarrhea, episodic anaphylactoid attacks), skin disease such as urticaria pigmentosa, and/or organ dysfunction from mast cell tissue infiltration. In general, antihistamines and cromolyn sodium are equally effective (or ineffective) in controlling mast cell degranulation symptoms.[27] Urticaria pigmentosa and pruritus respond modestly to topical corticosteroids or ultraviolet A phototherapy with (PUVA) or without (UVA1) psoralen.[28-31] We also consider interferon-α therapy for mast cell degranulation symptoms and urticaria pigmentosa that are refractory to usual therapy.[32]

The presence of organ dysfunction (e.g. symptomatic hepatosplenomegaly, clinically-significant liver function test abnormalities, ascites, cytopenias, osteoporosis or osteolysis, diarrhea associated with weight loss) distinguishes indolent from aggressive systemic mastocytosis. In general, we try to avoid the use of cytoreductive agents in patients with *indolent* systemic mastocytosis, where survival is usually long and disease course non-progressive.[33-35] By contrast, cytoreductive therapy is usually employed in aggressive systemic mastocytosis with the intention to decrease mast cell burden. Here, interferon-α and cladribine are the first-line drugs of choice and we expect response rates of >50% with each drug.[36,37] Treatment with either interferon-α or cladribine has the potential to benefit all aspects of disease, including mast cell degranulation symptoms, urticaria pigmentosa, symptomatic organomegaly and ascites. In the presence of osteoporosis or lytic bone lesions, we recommend, in addition, bisphosphonate therapy (e.g. pamidronate 90 mg IV monthly).[38,39]

Unfortunately, current therapy for patients with systemic mastocytosis who fail treatment with either interferon-α or cladribine is inadequate and we highly recommend that such patients participate in experimental treatment protocols. In this setting, *in vitro* activity against *KIT*D816V or *KIT*D814Y has been demonstrated for several kinase inhibitors such as PKC412,[40,41] dasatinib,[42,43] EXEL-0862,[44] SU5416,[45] SU6577,[46] MLN518[47] and other drugs including 17-AAG (binds heat-shock protein 90),[48] IMD-0354 (an NF-κB inhibitor)[49] and rapamycin (an mTOR inhibitor).[50] Of relevance to the latter agent, PI3K/Akt signaling has been implicated in mutant KIT-associated cell transformation and rapamycin has been shown to induce apoptosis in D816V-positive mast cell lines, inhibit survival of D816V-positive but not wild-type primary cells from patients with systemic mastocytosis, and suppress ligand-independent growth of *KIT*D814V-expressing cell lines.[50-52] Phase II clinical trials in systemic mastocytosis involving several of the aforementioned drugs (e.g. dasatinib, PKC412, and RAD001, a rapamycin analog) are currently ongoing.[53]

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