Tyrosine Kinase Inhibition in Mastocytosis

KIT and Beyond *KIT*

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KEYWORDS

• Mast cells • Mastocytosis • *KIT* mutations • Advanced disease
• Tyrosine kinase inhibitors • Targeted drugs • Drug development

KEY POINTS

- Mastocytosis is a group of orphan diseases characterized by abnormal accumulation/proliferation of mast cells in one or several organs.
- In adults, mastocytosis is mostly systemic and chronic, affecting the bone marrow and other internal organs, with or without skin involvement.
- Indolent systemic mastocytosis (SM) is usually well controlled by symptomatic therapy, whereas, in advanced SM, cytoreductive drugs are needed.
- In most patients with SM, a recurrent activating *KIT* mutation (D816V) is found in the neoplastic mast cells.
- In advanced SM, patients may benefit from treatment by KIT-targeting tyrosine kinase inhibitors; but new targeted drugs or drug combinations are still needed to improve patients' outcome.

INTRODUCTION

Mast cells (MCs) are hematopoietic stem cells–derived tissue resident granulated cells found close to blood vessels, nerves, and mucosal surfaces, such as respiratory and gastrointestinal (GI) tracts.[1] The major growth and differentiation factor for the MC lineage is stem cell factor (SCF), which binds KIT, a transmembrane receptor with intrinsic tyrosine kinase (TK) activity (**Fig. 1**).[2]

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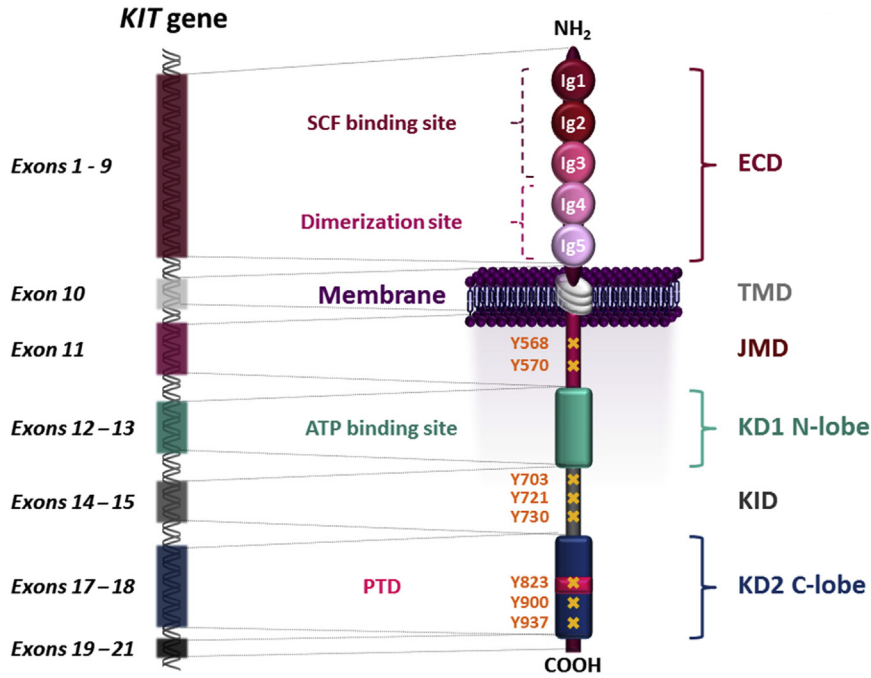

Fig. 1. Structure of the human normal *KIT* gene and of the corresponding KIT receptor. The *KIT* gene (*left*) contains 21 exons, encoding for a 145 kDa transmembrane protein, namely, the KIT receptor (*right*). KIT is represented in its monomeric form with its major structural and functional domains. The extracellular domain (ECD) is made by a longitudinal arrangement of 5 immunoglobulin-like (Ig-like) domains; the first 3 Ig-like domains of the ECD bind the SCF, whereas Ig-like domain 4 and 5 are involved in the dimerization process. The transmembrane domain (TMD) is composed of a hydrophobic α-helix allowing insertion of the receptor into the plasma membrane. The intracellular region contains the auto-inhibitory juxta-membrane domain (JMD) and a kinase domain (KD) divided by an insert region called kinase insert domain (KID) into a proximal N-lobe (KD1), which binds adenosine triphosphate (ATP) and a distal C-lobe, which contains the phosphotransferase domain (PTD). Yellow crosses indicate the position of the 8 tyrosine residues, which are phosphorylated upon activation of the receptor after ligation of SCF and dimerization.

Mastocytosis is a group of orphan diseases characterized by abnormal expansion of neoplastic MCs in at least one organ or tissue.[3] The most frequently affected organs/tissues are skin, bone marrow (BM), and GI tract.[3] Mastocytosis can affect both children and adults, with mostly pure cutaneous involvement in children, whereas systemic involvement is usually found in adults.[3] Most pediatric cases tend to resolve at adolescence, although some cases persist into adulthood.[3] By contrast, adult patients usually present with a chronic and indolent disease (indolent systemic mastocytosis [ISM]).[3] However, in some adult patients, more advanced subtypes of systemic mastocytosis (SM) may be diagnosed, for example, aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and MC leukemia (MCL).[3,4] Aggressive SM, SM-AHN, and MCL are collectively termed advanced SM (advSM). In ISM, clinical signs and symptoms are mostly related to increased mediator release by neoplastic MCs, whereas in advSM mediator–related symptoms are accompanied by organs damages following infiltration by neoplastic MCs.[3]