Advanced systemic mastocytosis: from molecular and genetic progress to clinical practice

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Systemic mastocytosis is a heterogeneous disease characterized by the accumulation of neoplastic mast cells in the bone marrow and other organ organs/tissues. Mutations in KIT, most frequently KIT D816V, are detected in over 80% of all systemic mastocytosis patients. While most systemic mastocytosis patients suffer from an indolent disease variant, some present with more aggressive variants, collectively called ”advanced systemic mastocytosis”, which include aggressive systemic mastocytosis, systemic mastocytosis with an associated hematologic, clonal non mast cell-lineage disease, and mast cell leukemia. Whereas patients with indolent systemic mastocytosis have a near normal life expectancy, patients with advanced systemic mastocytosis have a reduced life expectancy. Although cladribine and interferon-alpha are of benefit in a group of patients with advanced systemic mastocytosis, no curative therapy is available for these patients except possible allogeneic hematopoietic stem cell transplantation. Recent studies have also revealed additional somatic defects (apart from mutations in KIT) in a majority of patients with advanced systemic mastocytosis. These include TET2, SRSF2, ASXL1, RUNX1, JAK2, and/or RAS mutations, which may adversely impact prognosis and survival in particular systemic mastocytosis with an associated hematological neoplasm. In addition, several additional signaling molecules involved in the abnormal proliferation of mast cells in systemic mastocytosis have been identified. These advances have led to a better understanding of the biology of advanced systemic mastocytosis and to the development of new targeted treatment concepts. Herein, we review the biology and pathogenesis of advanced systemic mastocytosis, with a special focus on novel molecular findings as well as current and evolving therapeutic options.
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