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Review Article

KIT Inhibitors for the Treatment of Advanced Systemic Mastocytosis: Focus on the Elderly Patients

Guan-Jhe Tsai [a], Ken-Hong Lim [a,b,c *]

[a] *Division of Hematology and Oncology, Department of Internal Medicine, MacKay Memorial Hospital, Taipei City, Taiwan,* [b] *Department of Medicine, MacKay Medical College, New Taipei City, Taiwan,* [c] *Laboratory of Good Clinical Research Center, Department of Medical Research, MacKay Memorial Hospital, New Taipei City, Taiwan*

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SUMMARY

Mastocytosis is a myeloid neoplasm resulting from the excessive proliferation and accumulation of neoplastic mast cells in one or more organs. Systemic mastocytosis (SM) is a clonal hematopoietic stem cell neoplasm and a heterogeneous disease with several distinct subtypes. The majority of SM subtype in elderly patients belongs to advanced SM. Clinically, elderly patients with advanced SM carry a poor prognosis despite the use of cytoreductive therapy. Treatment with KIT tyrosine kinase inhibitors such as midostaurin and avapritinib has improved the outcome of advanced SM patients. The safety and efficacy of KIT inhibitors were reviewed, and the future direction of clinical development was discussed.

1. Introduction

Mastocytosis is a clonal myeloid neoplasm resulting from the excessive proliferation and accumulation of neoplastic mast cells in one or more organs. Beginning in the 2016 World Health Organization (WHO) classification of myeloid neoplasms, mastocytosis is classified as a distinct disease category based on its unique clinicopathologic characteristics.[1,2] When the involvement of mastocytosis is limited to the skin, it is termed cutaneous mastocytosis (CM). Whereas systemic mastocytosis (SM) is a clonal hematopoietic stem cell neoplasm characterized by the accumulation of neoplastic mast cells in one or more extra-cutaneous organs such as the bone marrow, liver, spleen, or gastrointestinal tract.[3] SM is a heterogeneous disease with several distinct subtypes: bone marrow mastocytosis, indolent SM (ISM), smoldering SM, aggressive SM (ASM), and SM with an associated hematologic neoplasm (AHN), and mast cell leukemia (MCL).[3–8] Due to the poor prognosis of these patients, aggressive SM, SM-AHN, and MCL are grouped as advanced SM.[4] CM and ISM are primarily diagnosed in children and young adults, and the clinical course is usually indolent and self-limited in most patients. However, the majority of SM subtype in elderly patients belongs to advanced SM (62% to 89%) with poor outcome.[9,10] In a Mayo Clinic series of 342 patients with SM, the median survival of ASM, SM-AHN, and MCL are 41 months, 24 months, and two months, respectively.[4]

2. Epidemiology

A retrospective nationwide population-based epidemiological study of mastocytosis from Denmark reported the incidence rate for SM was 0.89 per 100,000 per year.[11] In this study, urticaria pigmentosa (a form of CM) was the most common subtype (50%), followed by ISM (32%), SM with subtype unknown (11%), SM-AHN (4%), ASM (2%), and MCL (1%). One-fifth (20%) of the patients were elderly (age ≥ 65-year-old) in this study (Table 1). The distribution of SM subtypes in elderly patients was indolent SM (39%), urticaria pigmentosa (32%), SM with subtype unknown (16%), SM-AHN (6%), ASM (4%), and MCL (4%).

3. Molecular pathogenesis

KIT D816V mutation is a driver mutation for SM and can be detected in more than 90% of patients. The frequency of *KIT* D816V mutation in the elderly patients is also similar to the overall patient population and ranges from 82 to 85%.[9,10] Interestingly, multilineage involvement of *KIT* D816V could be identified in variable myeloid subtypes in advanced SM.[12] Also, somatic mutations in other myeloid malignancy-related genes such as *SRSF2*, *ASXL1*, *RUNX1*, and *TET2* are frequently detected in ~90% of advanced SM patients suggesting that advanced SM is a multi-mutated disease.[12–14] In the study by Rouet et al., 17 of 26 (65.3%, 2 ASM, 14 SM-AHD, and 1 MCL) of their elderly patients harbored additional mutations in

Table 1
The distribution of mastocytosis by subtype in different age groups in Denmark, 1997–2010.[11]

Age (year)	UP	ISM	SM (subtype unknown)	ASM	SM-AHN	MCL	Total case (%)
15–44	124	69	11	2	3	0	209 (38.1)
45–64	117	62	33	2	15	1	230 (42.0)
≥ 65	35	43	17	4	6	4	109 (19.9)

Abbreviations: ASM, aggressive systemic mastocytosis; ISM, indolent systemic mastocytosis; MCL, mast cell leukemia; SM, systemic mastocytosis; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm; UP, urticaria pigmentosa.

* Corresponding author. Division of Hematology and Oncology, Department of Internal Medicine, MacKay Memorial Hospital, Taipei, Taiwan.
E-mail address: limkenhong@gmail.com (K.-H. Lim)

other myeloid malignancy-related genes including *TET2*, *SRSF2*, *IDH2*, and *ASLX1* mutations.[10] All of the above-mentioned mutations may co-occur with *KIT* D816V in the same cells or may be expressed in other myeloid cells but not in mast cells. Notably, these mutations were frequently found to precede the *KIT* D816V mutation indicating that *KIT* mutation is often a late event conferring a mastocytosis phenotype on a pre-existing clonal condition.[12] With the use of single-cell DNA sequencing, this observation was clearly demonstrated in an elderly patient with advanced SM who had a *RUNX1* mutation preceded the *KIT* D816V mutation.[15] The presence and number of mutated genes in the *SRSF2*/*ASXL1*/*RUNX1* (*S*/*A*/*R*) gene panel have also been shown to be independent adverse prognostic factors in advanced SM.[13,14,16,17]

4. Diagnosis

The diagnosis of SM is based on the fulfillment of the updated 2022 WHO diagnostic criteria for SM as listed below (adapted from[6–8]). The major criterion and one minor criterion or at least three minor criteria are required to establish the diagnosis of SM.

4.1. Major criterion

Presence of multifocal, dense infiltrates of abnormal mast cells (≥ 15 mast cells in clusters) in the bone marrow and/or extracutaneous organ(s).

4.2. Minor criteria

a. In bone marrow or other extracutaneous organ(s), > 25% of the mast cells in the infiltrate have atypical morphology or are spindle-shaped (type I or type II).
b. Presence of *KIT* D816V mutation or other rare activating *KIT* alterations in bone marrow, blood, or other extracutaneous organ(s).
c. Mast cells in bone marrow, blood or other extracutaneous organ(s) aberrantly express CD25, CD2, and/or CD30.
d. Elevated serum tryptase level over 20 ng/mL when there is absence of an associated myeloid neoplasm. In patients with hereditary alpha-tryptasemia, the tryptase level should be adjusted.

The diagnosis of SM-AHD requires meeting criteria for SM and criteria for an associated hematologic neoplasm (such as myeloproliferative neoplasm, myelodysplastic syndrome, acute myeloid leukemia, or other hematologic neoplasm defined by the WHO classification as a distinct entity). ASM is diagnosed when SM patients present with one or more "C" findings, and the diagnosis of an associated hematologic neoplasm or MCL is not fulfilled. C-findings are organ damage attributable to neoplastic mast cell infiltration and include osteolyses or severe osteoporosis causing pathologic fractures, palpable splenomegaly with hypersplenism, hepatomegaly with ascites and/or impaired liver function, malabsorption with hypoalbuminemia and weight loss, cytopenia(s) (absolute neutrophil count < 1000/μL or hemoglobin < 10 g/dL or platelets < 100,000/μL), and life-threatening organopathy in other organ systems caused by the infiltration of the organ(s) by neoplastic mast cells.[1,2,18] MCL is diagnosed when the bone marrow biopsy of SM patients reveals diffuse infiltration by atypical, immature mast cells, and the bone marrow aspirate smears show 20% or more mast cells.

5. Clinical presentation

SM has a heterogeneous clinical presentation. The symptoms of SM include pruritus, flushing, diarrhea, syncope, anaphylaxis, bone pain, osteoporosis, and constitutional symptoms depending on the involvement of various organs in the body. Hepatomegaly, splenomegaly, lymphadenopathy, ascites, abnormal liver function, anemia, thrombocytopenia, eosinophilia, or leukoerythroblastosis may be present especially in adult patients with advanced SM.[4] These symptoms and signs are caused by the release of mast cell mediators or the direct involvement of organs by neoplastic mast cells. The diagnosis of SM in elderly patients is usually delayed, and they often present with poor performance status, hepatosplenomegaly, osteoporosis with fractures, cytopenia, and symptoms of mast cell activation.[9,10,19,20] According to one study, the median time to diagnosis of SM in elderly patients was estimated at 9 months (range, 3 to 12 months) from the onset of systemic signs.[10]

6. Treatment for advanced SM

Symptomatic treatments are frequently used in patients with SM. Antihistamines, proton pump inhibitors, mast cell stabilizers, bisphosphonates and/or low doses of corticosteroids can be used to control various symptoms of elderly SM patients.[18] Best supportive care including transfusion is also important in this population. Cytoreduction is indicated in SM patients either due to refractory symptoms and/or the aggressiveness of the disease. Interferon (IFN)-α with or without oral corticosteroids (prednisone/prednisolone),[21–26] cladribine (2-CdA)[27–29] and hydroxyurea[26] have been used with various success in advanced SM patients.

Imatinib mesylate is the first small-molecule targeted therapy that has shown clinical efficacy usually in SM patients with certain trans-membrane and juxta-membrane KIT mutants such as the Phe522Cys mutation,[26,30–34] and in those with wild-type KIT.[35] Recently, the multikinase inhibitor midostaurin has been approved for treating adults with advanced SM based on the significant clinical activity in a single-arm, open-label study in 116 adults with advanced SM.[36] Midostaurin was administered at 100 mg orally twice daily in 28-day cycles until disease progression or intolerable toxicity. The overall response rate was 60%, and 45% of the patients had a major response. The median progression-free survival and overall survival in this cohort of advanced SM were 14.1 months and 28.7 months, respectively. It is noteworthy that age as a continuous variable was not associated with overall survival in the primary efficacy population in this study. Midostaurin at 100 mg twice daily by mouth was also studied in another single-arm, multicenter, open-label trial of 26 patients with advanced SM.[37] The median age in this latter study was 64 years. In 10 of the 17 patients with SM-AHN, 1 achieved partial response and 9 achieved major response by 2 cycles that was sustained for at least 8 weeks. In 2 of the 6 patients with MCL, 1 had partial response and 1 had major response. The median duration of response had not been reached for these 2 groups of patients. Midostaurin was then approved for the treatment of adults with advanced SM by the U.S. Food and Drug Administration in April 2017.[36,37] The most frequent side effects of midostaurin in advanced SM patients were gastrointestinal symptoms including nausea, vomiting, diarrhea, abdominal pain, edema, musculoskeletal pain, and fatigue. In the above-mentioned 2 clinical studies of midostaurin in advanced SM, 64 (45%) of the 142 patients were ≥ 65 years old including 16 (11%) were ≥ 75 years old.[38] Overall, there were no significant differences in safety or response rate observed between the elderly patients when compared with younger patients. However, the use of midostaurin and other targeted therapy for elderly patients with advanced SM should be cautious, because of the greater frequency of co-morbidity or other drug treatment in this population.

Currently, both primary and acquired resistance to midostaurin is a clinical challenge in treating advanced SM. The complexity and dynamics of mutational profiles in midostaurin-treated advanced SM have been studied using serial next-generation sequencing (NGS) analysis by Jawhar et al.[39] They found that acquisition of additional mutations or increasing variant allele frequency (VAF) in *K/NRAS*, *RUNX1*, *IDH2*, or *NPM1* were associated with progression. However, the changes in clonal architecture under the selection pressure of KIT inhibition in advanced SM are still elusive. In contrast to traditional bulk DNA sequencing, molecular analysis at the single-cell level will provide a better opportunity to resolve clonal architecture in complex diseases.

In addition, avapritinib is a selective KIT and platelet-derived growth factor receptor alpha (PDGFRA) kinase inhibitor with potent KIT D816V inhibitory activity. Avapritinib was initially approved for treating gastrointestinal stromal tumors bearing a *PDGFRA* exon 18 mutation. The US FDA approved avapritinib for the treatment of advanced systemic mastocytosis in 2021.[40–42] The safety and efficacy of avapritinib were investigated in two pivotal clinical trials (EXPLORER and PATHFINDER) in patients with advanced systemic mastocytosis. The EXPLORER study was a multicenter, phase I study in adult patients with advanced systemic mastocytosis beginning in 2016.[43] Dose escalation and expansion were evaluated in 69 patients, and overall response to therapy was determined according to the International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (IWG-MRT-ECNM) protocol. Thirty-nine patients with advanced systemic mastocytosis were available for evaluation, and an overall response rate of 77% (30/39 patients) was found in these patients. The overall survival rate was 78% in all patients with advanced systemic mastocytosis at 24 months. Patients with the S/A/R panel mutations that are known to carry a poorer prognosis also experienced good clinical response with avapritinib [73% (16/22) overall response rate]. The most frequent adverse effects of avapritinib were limited and nonspecific gastrointestinal symptoms. Approximately 10% of SM patients experienced mild to moderate pancytopenia.

Another phase 2 study of avapritinib in advanced SM was the PATHFINDER trial which was designed to evaluate overall response rates, survival, and quality of life measured in patients with advanced SM.[44] In the PATHFINDER study, 62 patients with median age of 69 years (range 31–88) were enrolled and avapritinib was given at 200 mg daily. The interim analysis of this study found a 75% overall response rate in patients with advanced SM. Only 8% of patients discontinued the study due to adverse effects. This study showed that avapritinib was effective in the elderly patients with advanced SM. In the 2 above-mentioned clinical studies involving 131 patients with advanced SM, 62% were $\geq$ 65 years old including 21% were $\geq$ 75 years old.[45] No significant differences in safety or efficacy were observed between the elderly patients when compared with younger patients.

7. Conclusions

The majority of SM subtype in elderly patients belongs to advanced SM. Clinically, elderly patients with advanced SM usually have a poor clinical outcome despite the use of cytoreductive therapy. KIT tyrosine kinase inhibitors such as midostaurin and avapritinib have been approved to treat advanced SM patients resulting in the improvement of clinical response and survival. Newer and more selective KIT kinase inhibitors are being developed to improve treatment efficacy and decrease toxicity. The outcome of elderly patients with advanced SM is improving. For those elderly patients who cannot achieve durable remissions with KIT inhibitors, cladribine, interferon-alpha and best supportive care are other options that can be considered.[26,27,46,47]

Conflicts of interest

We declare no conflicts of interest relevant to this study.

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