Experience of Patients With Smoldering Systemic Mastocytosis Treated With Avapritinib as Part of a Global Compassionate Use Program

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Introduction

- Systemic mastocytosis (SM), a myeloid neoplasm driven by the *KIT* D816V mutation in ~95% of cases, is characterized by the accumulation of neoplastic mast cells (MCs) in the bone marrow (BM), skin, and other organs[1,2]
- Diagnosis of SM based on World Health Organization (WHO) criteria includes presence of 1 major and 1 minor criterion, or ≥3 minor criteria (**Table 1**)[3–8]
- SM can be divided into
  - 1) advanced SM (AdvSM) comprised of aggressive SM (ASM), SM with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL),[9] and
  - 2) non-advanced SM comprised of indolent SM (ISM) which represents 90–95% of all patients with non-advanced SM and the smoldering SM (SSM) variant (**Table 1**)[10,11]
- The SSM variant is characterized by the presence of ≥2 "B-findings" and the absence of "C-findings" (**Table 1**).[4] Patients with SSM can progress to AdvSM or transform to leukemia in ~9% of cases[10,11] and demonstrate worse survival when compared with patients with ISM[3]
- Currently, there are no approved therapies for patients with SSM.[3] The National Comprehensive Cancer Network (NCCN) guidelines recommend management of MC symptoms with anti-mediator treatment or participation in a clinical trial for patients with SSM[12]
- Avapritinib is an oral, highly potent and selective inhibitor of KIT D816V, other KIT exon 17 mutations, and homologous platelet-derived growth factor alpha (PDGFRα) exon 18 mutations[13]
- Avapritinib 200 mg once daily (QD) is approved by the US Food and Drug Administration for the treatment of adult patients with AdvSM,[14] and by the European Medicines Agency for the treatment of adults with ASM, SM-AHN, or MCL, after at least one systemic therapy.[15] It has been included in the latest version of the NCCN SM treatment guidelines for patients with AdvSM[12]
  - Avapritinib is also approved in the USA for the treatment of gastrointestinal stromal tumors (GIST) harboring a *PDGFRα* exon 18 mutation[14] and in the EU for GIST harboring a *PDGFRα* D842V mutation[16]
- Here we report on the experience of 15 patients with SSM treated with avapritinib in the Compassionate Use Program (CUP)

Table 1: Diagnostic criteria for SM and subtypes[3,4]

Diagnostic criteria for SM

Major Criterion
- Multifocal, dense infiltrates of MCs (≥15 MCs in aggregates) detected in BM and/or other extracutaneous organs

Minor Criterion
- Atypical MC morphology (>25% of the MCs in the infiltrate are spindle-shaped or have atypical morphology or, of all mast cells in bone marrow aspirate smears, >25% are immature or atypical)
- Expression of CD25 with or without CD2
- Detection of the *KIT* D816V mutation in BM, blood, or other extracutaneous organ
- Serum tryptase level of >20 ng/ml without associated myeloid neoplasm

B-findings
- High MC burden shown on BM Biopsy: >30% infiltration of cellularity by MCs and serum total tryptase level >200 ng/ml
- Evidence of dysplasia or myeloproliferation, in non-MC lineage(s), but insufficient criteria for definitive diagnosis of an AHN, with normal or only slightly abnormal blood counts
- Hepatomegaly without impairment of liver function, palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging

C-findings
- BM dysfunction caused by neoplastic MC infiltration, manifested by ≥1 cytopenia(s) (ANC <1.0 × 10^9/L, Hgb <10 g/dL, and/or platelet count <100 × 10^9/L)
- Palpable hepatomegaly with impairment of liver function, ascites and/or portal hypertension
- Skeletal involvement with large osteolytic lesions with/without pathological fractures
- Pathological fractures caused by osteoporosis do not qualify as a "C-finding"
- Palpable splenomegaly with hypersplenism
- Malabsorption with weight loss due to gastrointestinal MC infiltrates

Diagnostic criteria for SM subtypes

Advanced SM (ASM, SM-AHN, and MCL)	Non-Advanced SM (ISM and SSM)
ASM • Meets diagnostic criteria for SM • Has 1 or more "C-findings" • No evidence of MCL	**ISM** • Meets criteria for SM • No "C-findings" or evidence of AHN • 0–1 "B-findings" • Isolated BM mastocytosis • Low burden of MC
SM-AHN • Meets diagnostic criteria for SM and criteria for AHN as a distinct entity per the WHO classification	**SSM** • High burden of MC defined by the presence of ≥2 "B-findings"
MCL • Meets diagnostic criteria for SM • BM biopsy shows diffuse atypical, immature MC infiltration • BM aspirate with ≥20% MCs	

AHN, associated hematological neoplasm; ANC, absolute neutrophil count; ASM, aggressive systemic mastocytosis, BM, bone marrow; Hgb, hemoglobin; ISM, indolent systemic mastocytosis; MC, mast cell, MCL, mast cell leukemia; SM, systemic mastocytosis; SM-AHN, systemic mastocytosis with an associated hematological neoplasm; SSM, smoldering systemic mastocytosis.

Methods

- The CUP is an ongoing, global, open-label access program (January 2018 to present). Data shown here includes patients who approved and initiated treatment as of October 15, 2021, with data presented through individual patients' most recent shipment of medication (latest February 9, 2022)
- The CUP provides avapritinib to eligible patients who meet the following criteria:
  - Patients diagnosed with AdvSM, SSM, or other tumor types with mutation(s) in exon 17 of the *KIT* gene or in exon 18 of the *PDGFRα* gene
  - Patients who received all available standard therapies or are not a candidate for the available standard therapies
  - Patients who are ineligible or unable to access an ongoing avapritinib clinical trial, or patients seeking treatment where avapritinib is not commercially available
  - Patients with platelets below 50,000/μL were excluded

Results

- Fifteen patients diagnosed with SSM according to the treating physician were enrolled into the CUP including 13 patients with *KIT* mutations (**Table 2**)

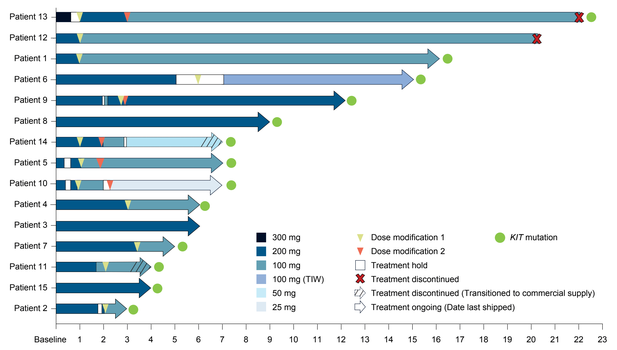
Table 2. Patient demographics (N=15)

Demographic	Patients all doses (N=15)
Median age, years	56
<65 years, n (%)	4 (27)
>65 years, n (%)	11 (73)
Female, n (%)	7 (47)
Male, n (%)	8 (53)
Region, n (%)	
Australia	1 (7)
North America	7 (47)
Europe	4 (27)
UK	3 (20)
Prior therapies	
Midostaurin	6 (40)
Interferon	6 (40)
Imatinib	3 (20)
Cladribine	3 (20)
Other TKIs[a]	3 (20)
Mutation analysis	
KIT mutation	13 (87)
No *KIT* mutation	1 (7)
Not available	1 (7)

[a]Dasatinib (n=1), masitinib (n=1), nilotinib (n=1)

- A total of 14 patients received avapritinib starting dose of 200 mg QD and 1 patient received 300 mg QD. Overall, three patients remained at 200 mg QD without any dose modifications (**Figure 1**)
- Currently, 11 patients are continuing treatment in the CUP with an average treatment duration (from last date shipped) of 8.2 months
- Clinical parameters for all patients are shown in **Table 3**
- The 4 patients who discontinued from the CUP received avapritinib for an average of 13 months. One patient discontinued treatment due to disease progression, 2 patients transitioned to commercial product, and 1 patient was lost to follow-up; no patients discontinued due to adverse events
- Dose interruptions were done in 7 patients (low platelets, n=2; periorbital edema, conjunctivitis, and headache, n=1; asthenia and flushing, n=1; anemia, n=1; memory impairment, facial/periorbital edema, tremors, dizziness, abdominal pain, nausea, and vomiting; n=1; esophageal stricture, n=1) and dose reductions were done in 12 patients
- Most patients maintained platelet counts well above thrombocytopenia threshold (**Figure 2**)

Figure 1. Avapritinib treatment duration and dosing changes over time per individual SSM patient (N=15)



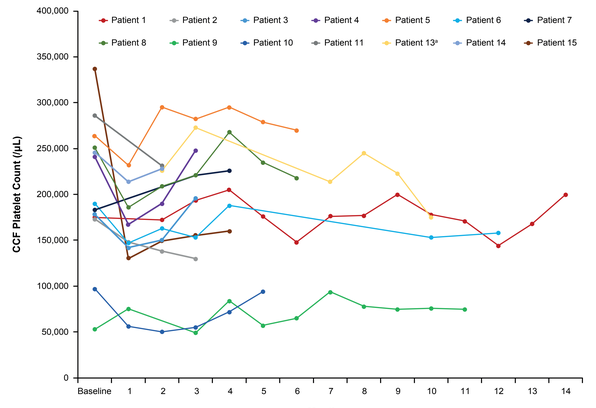
SSM, smoldering systemic mastocytosis; TIW, three times a week.

Table 3. Clinical parameters of individual patients (N=15)

Patient (ID)	Treatment duration[a] (months)	*KIT* mutation[b] (Y/N)	Current dose	Prior anti-neoplastic therapies (n)	Additional relevant information
1	16	Y	100 mg	None	BM MC infiltrate (50%); tryptase 164 ng/ml; splenomegaly, bone lesions and urticaria pigmentosa; radiological evidence of osteoporosis
2	3	Y	100 mg	None	BM MC infiltrates(>30%); GI MC infiltration; tryptase >200 ng/ml; myelodysplasia without overt ahn; abdominal lymphadenopathy
3	6	N	200 mg	Cladribine	BM MC infiltrates; MC infiltrates in skin; daily flushing and sweating; explosive diarrhea; urticaria exacerbated by heat, exercise and shower
4	6	Y	100 mg	Masitinib	BM MC infiltrates (50%),tryptase 560 ng/ml; psychiatric manifestations and cognitive decline; anaphylaxis to hymenoptera
5	7	Y	100 mg	Interferon; midostaurin; cladribine	BM MC infiltrates; tryptase 1089 ng/ml; frequent daily diarrhea; asthenia and dyspnea
6	15	Y	100 mg (3x a week)	Imatinib; pegylated interferon	BM MC Infiltrate (40%); tryptase >200 ng/ml; splenomegaly with no organ damage; idiopathic anaphylaxis
7	5	Y	100 mg	Interferon	BM MC infiltrates (35%); tryptase 250 ng/ml; small lytic lesions and bone pain; hepatomegaly/splenomegaly
8	9	Y[c]	200 mg	Nilotinib; pegylated Interferon	Disabling mediator symptoms; intolerant to all anti-mediator therapies
9	12	Y[c]	200 mg	Imatinib; midostaurin	BM MC infiltrate with fibrosis; low risk MDS with *TET2* and *SRSF2* mutations; normal karyotype
10	7	Y	25 mg	None	BM MC infiltrates; tryptase >200 ng/ml; progressive splenomegaly; diffuse skeletal changes consistent with osteoporosis
11	4	Y	DC (transitioned to commercial supply)	Dasatanib; cladribine; midostaurin	BM MC infiltrates (40%); tryptase 327 ng/ml; frequent anaphylaxis
12	20	NA	DC (disease progression)	Imatinib; midostaurin; interferon	Failed all prior therapies; continues to experience symptoms of disease
13	22	Y	DC (lost to follow-up)	None	BM MC infiltrates (40%); secondary myelofibrosis; tryptase >200 ng/ml; minimal splenomegaly; skin and GI symptoms; fatigue
14	7	Y	DC (transitioned to commercial supply)	Midostaurin	BM MC Infiltrate (80%); tryptase 915 ng/ml; hepatomegaly/splenomegaly; skin rash, nausea, vomiting, diarrhea, abdominal pain
15	4	Y	200 mg	Midostaurin; interferon	MC infiltrates in BM, skin and GI tract; inadequate control of debilitating constitutional symptoms despite maximal supportive case with mast cell stabilizers

[a]From last shipment date; [b]KIT D816V, unless otherwise specified; [c]Specific KIT mutation not specified. AHN, associated hematologic neoplasm; BM, bone marrow; DC, discontinued; GI, gastrointestinal; MC, mast cells; MDS, myelodysplastic syndrome; NA, not available.

Figure 2. Change in platelet counts (per μL) in patients (N=14) with SSM treated with avapritinib



[a]Patient 13's first measurement was 2 months after treatment initiation. CCF, Platelet count calculation formula; SSM, smoldering systemic mastocytosis

Conclusions

- For SSM patients with no approved therapeutic options, the avapritinib CUP program provides access to treatment
- In 14 patients with tests reported, 13 were positive for *KIT* mutation; 1 patient did not have test results available
- 11 of 15 patients had previously been treated with anti-neoplastic therapies
- In patients with investigator-diagnosed SSM, treatment with avapritinib was managed with dose modifications/reductions for expected treatment-related adverse events
- Only two patients had baseline thrombocytopenia, and in general, individual platelet levels have been consistent over time
- Of the 4 patients who discontinued from the CUP, 2 transitioned to commercial supply and continued treatment, 1 was lost to follow-up, and 1 showed disease progression

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Disclosures

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