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Avapritinib treatment of aggressive systemic mastocytosis with a novel KIT exon 17 mutation

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A B S T R A C T

Background: Systemic mastocytosis is a rare hematologic malignancy that leads to the accumulation of neoplastic mast cells in the bone marrow, visceral organs, and skin. Mutations in the receptor tyrosine kinase, KIT are seen in most patients with systemic mastocytosis. The most common mutation is a gain of function mutation in KIT D816V. Avapritinib is a highly selective KIT D816V inhibitor approved for the treatment of advanced systemic mastocytosis. Recent studies have also suggested that avapritinib is active across other KIT mutations located in exon 11 and exon 17.

Case Presentation: A 68 year old woman was referred for a history of lymphadenopathy and diarrhea and was ultimately found to have systemic mastocytosis with involvement in her bone marrow, gastrointestinal tract, liver, and spleen. The bone marrow biopsy reveled a novel KIT p.D816-N822delinsMIDSI mutation in exon 17. The patient was started on avapritinib leading to significant decrease in the frequency of her diarrhea and a significant reduction in her tryptase levels. Her course was complicated by arthralgias leading to a decrease in her avapritinib dose and ultimately a degranulation episode requiring hospitalization. Following dose re-escalation, patient has remained clinically stable without any further adverse events.

Conclusion: We report a case of aggressive systemic mastocytosis with a novel KIT mutation on exon 17 treated with avapritinib leading to a sustained response. While avapritinib is known as a potent inhibitor against the D816V mutation, our case suggests that it may also be effective against other rare KIT mutations in systemic mastocytosis offering more potential treatment options in patients with rare mutations.

Systemic mastocytosis (SM) is a rare hematologic malignancy characterized by a clonal expansion of mast cells (MC) [1]. This abnormal growth and accumulation of neoplastic mast cells can involve various tissues, and commonly affects bone marrow, visceral organs, and the skin [1]. The World Health Organization (WHO) has classified SM into six different categories: bone marrow mastocytosis, indolent SM (ISM), smoldering SM (SSM), aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL) [2]. Of these entities, ASM, SM-AHN, and MCL are considered advanced forms of systemic mastocytosis.

Mutations in receptor tyrosine kinase KIT are seen in more than 90 % of patients with SM [3,4]. The most common mutation is a gain of function mutation in KIT D816V on exon 17 and leads to constitutive activation of KIT and proliferation of mast cells [5]. Other KIT mutations involving codon 816 are rare in SM and included D816A/F/H/I/N/T/Y [5,6]. These mutations function similarly to the D816 mutation leading to constitutive activation [5]. The KIT D816V mutation is also a common mutation in patients with ASM however molecular pathogenesis of this disease category is more complex. In addition to the KITD816V mutation in multiple lineages as opposed to only the mast cell lineage in ISM, patients with ASM often have additional driver mutations like TET2, SRSF2, ASXL1, RUNX1, JAK2 and N/KRAS [2,7–10].

Because of the frequency of KIT D816V mutation in SM and the role it plays in MC proliferation it is an attractive target. Based on NCCN guidelines, preferred treatment of ASM can be with midostaurin, avapritinib, or enrollment in a clinical study [11]. Other regimens include cladribine or PEG-interferon with prednisone [11]. Notably, imatinib is a treatment option for the <1 % of ASM cases that are KIT D816V negative [11]. Midostaurin a multi-kinase inhibitor with activity against KIT D816V, was approved in 2017 for the treatment of ASM based on an overall response rate of 60 % and major responses seen in 45 % of all patients [12].

Avapritinib is a highly selective KITD816V inhibitor with recent approval by the FDA for treatment of ASM. Two major trials led to the approval of avapritinib in the treatment of ASM. The phase 1 EXPLORER trial study demonstrated a 75 % overall response rate with a complete remission rate of 36 % and greater than 50 % reduction in marrow mast cells and serum tryptase in a majority of patients [13]. The phase 2 PATHFINDER trial demonstrated a 75 % overall response rate with similar reductions in serum tryptase, and bone marrow mast cells [14].

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TTTTGGTCTAGCCAGAGACATCAAGAATGATTCTAATTATGTGGTTAAAG
 F  G  L  A  R  D  I  K  N  D  S  N  Y  V  V  K  G   Wild-type

TTTTGGTCTAGCCAGAATGATCGATTCGATT------TATGTGGTTAAAG
 F  G  L  A  R  M  I  D  S  I  -  -  Y  V  V  K  G   p.816_N822delins MIDSI
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Fig. 1. Alignment of wild-type and novel mutant KIT sequences. The underlined amino acids highlight the differences between wild-type and mutated protein sequences. For orientation, the FG amino acids at the beginning of the sequence are the C-terminal portion of the classical kinase DFG motif. For the wild-type sequence, the first underlined amino acid (aspartic acid (D)) indicates the codon 816 position.

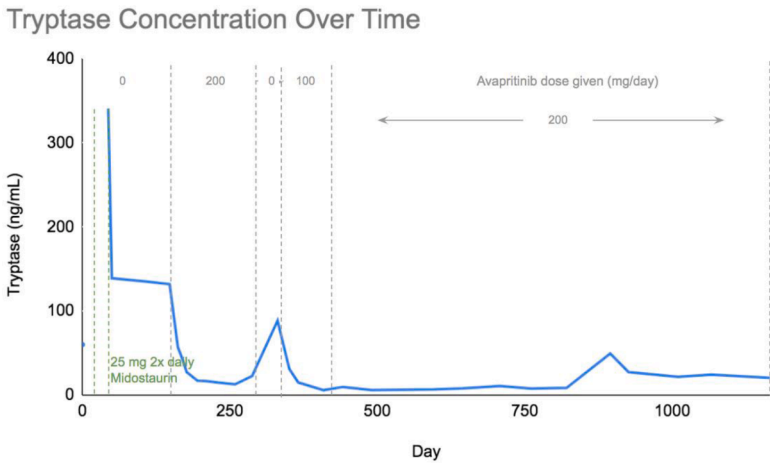

Fig. 2. Changes in tryptase concentration during treatment with avapritinib. The gray dotted lines indicate changes in avapritinib dosing with beginning of the graph and green dotted lines showing initial midostaurin treatment.

Avapritinib has also been shown to be active across other KIT mutations located in the juxtamembrane region in exon 11, as well as other mutations affecting the activation loop (exon 17) [15–17]. In this case study, we report a case of ASM without the KIT D816V mutation but a novel mutation in the same region treated with avapritinib with a clinical sustained response.

A 68 year old woman was referred for a history of lymphadenopathy and diarrhea. A bone marrow biopsy was completed which was notable for 20–30 % mast cell infiltrate. There was no evidence of immature mast cells. There was no evidence of associated hematologic malignancies (AHN) or mast cell leukemia (MCL). Minor findings included more than 25 % atypical mast cells and baseline tryptase more than 20 ng/ml. Further genetic testing revealed an activating KIT mutation leading to her diagnosis of systemic mastocytosis, thus representing a third minor finding. She was ultimately diagnosed with ASM based on positive C-findings of cirrhosis and malabsorption. Other biopsy proven organ involvement included extensive replacement of axillary lymph nodes by mast cells. The medical history was otherwise unremarkable. The patient's next generation sequencing of her bone marrow showed a novel KIT p.D816_N822delinsMIDSI mutation in exon 17 (Fig. 1) as opposed to the typical KIT D816V mutation [18,19]. The patient's tryptase was initially elevated at 60.1 ng/mL. Her liver enzymes were normal at diagnosis and she has a leukocytosis to 18.7 10^3/uL and thrombocytosis to 740 10^3/uL. The patient was started on midostaurin however after about 3 months of treatment, developed grade 4 pneumonitis leading to discontinuation of this agent. Prior to that patient continued to have symptoms of diarrhea and fatigue with a continued increase in her tryptase. Given the presumed activating nature of the patient's mutation, the decision was made to start treatment with avapritinib 200 mg daily. At this time she had leukocytosis to 15.3 10^3/uL, thrombocytosis to 889 10^3/uL and elevated alkaline phosphatase at 181 U/L with normal liver enzymes and an elevated tryptase of 132 ng/mL. At the patient's two week follow up she reported a significant decrease in the frequency of her diarrhea and her tryptase levels decreased by 50 % over the two weeks of treatment (Fig. 2). Over the following two weeks she developed grade 2 arthralgias and joint swelling which resolved with two rounds of steroids. At her follow up appointment, her labs continued to show a decrease in tryptase without any other evidence of adverse drug reactions. Follow up CT imaging showed a decrease in lymphadenopathy indicating an imaging response to the avapritinib. Over the first four months of treatment, the patient's tryptase levels continued to decrease and she experienced improvement of her symptoms, especially diarrhea. Her other adverse drug reactions remained minimal and included grade 1 and grade 2 periorbital edema, alopecia, concentration impairment, and depression which improved with steroids. Given the patients response to treatment over first 6 months, her avapritinib dose was decreased to 100 mg daily. Following this decrease, the patients tryptase levels started to increase and she was admitted to the hospital for hypotension from degranulation episodes thus prompting restarting on 200 mg daily and subsequent decrease in tryptase. Her course was further complicated by another hospitalization for urosepsis and anemia. Following avapritinib dose re-escalation, the patient has remained clinically stable with down trending of tryptase and cessation of degranulation events. Her diarrhea and GI symptoms almost completely resolved and you was able to discontinue supportive care for these symptoms. As of the time of last follow up, the patient has continued avapritinib 200 mg with good tolerance to therapy and improved symptoms. Serial next generation sequencing was not conducted on this patient to monitor mutation response as the patient declined serial bone marrow examinations.

As of December 2023, the COSMIC data base includes information on 125,000 human cancers with KIT sequencing results [20]. We identified 6 cases with insertion/deletion mutations around KIT codon 816: 1 case of p.L813_A814delinsSLL (AML), 1 cases of p.R815_D816delinsV (mast cell neoplasm), 2 cases of p.D816_I817delinsG (both AML), 1 case of p.K818_D820delinsN (GI stromal tumor), 1 case of p.S821_N822delinsGY (AML) [20]. In contrast, the data base includes almost 2000 cases of D816V, the vast majority identified in AML or mast cell neoplasms [20]. To further characterize this previously unreported KIT mutation, we cloned the mutation and stably transduced BaF3 cells and identified

numerous clones with IL-3 independent growth, confirming that this novel mutation results in constitutive KIT kinase activation and is a transforming oncogenic kinase [21]. We compared the drug sensitivity of BaF3 cells with the typical KIT D816V mutation with cells transformed by the novel mutation found in our patient. The imatinib IC_{50} for inhibition of KIT autophosphorylation was >500 nM for both cell lines, indicating extreme imatinib resistance. However, the IC_{50} for avapritinib was 10 and 65 nM for the D816V mutation and the MIDSI mutation, respectively, providing an explanation for the patient's clinical response to avapritinib.

Here we report on a case of aggressive SM with a novel KIT mutation and subsequent treatment with avapritinib and a sustained response. KIT D816V mutations are extremely common in SM and can be detected in greater than 90 % of cases [3,4]. Our patient carried a rare KIT p.D816_N822delinsMIDSI mutation that has not been previously reported. Based on the activating nature of the mutation, the decision was made to treat with the selective KIT D816V inhibitor, avapritinib and proved to be successful as evident by decreasing tryptase levels, improvement in symptoms, and decrease in lymphadenopathy. While avapritinib is known to be a potent inhibitor against the D816V mutation, our case suggests that this drug may also be effective against other rare KIT mutations in SM and could be considered as a possible treatment option in other cases with novel KIT mutations, involving KIT exon 17.

Informed consent

Case report reviewed by Oregon Health and Science University IRB. No PHI was obtained or shared. No identifiable objects were included in the report. The HIPPA waiver and Request for Determination were approved by the OHSU IRB.

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CRediT authorship contribution statement

Lyndsey Sandow: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Ajia Town:** Formal analysis. **Michael C. Heinrich:** Conceptualization, Formal analysis, Supervision, Writing – review & editing.

Declaration of competing interest

Dr. Michael Heinrich receives consulting fees from Novartis, Deciphera Pharmaceuticals, Blueprint Medicines, Cogent Pharmaceuticals, Cstone Pharmaceuticals, and Theseus Pharmaceuticals.

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