Telangiectasia macularis eruptiva perstans (TMEP) is a rare cutaneous mastocytosis that has a high frequency of progression to systemic disease, including aggressive systemic mastocytosis (ASM). We describe successful treatment of refractory TMEP that progressed to ASM in a 35-year-old woman who failed multiple lines of therapy until receiving a new targeted agent, avapritinib (BLU-285) in a clinical trial IRB 15-2178 on November 2016. Within 8 weeks of treatment with avapritinib, her symptoms resolved, and she achieved complete remission for over 3 years.

CASE

In 2007, a 35-year-old woman developed a pruritic rash on her left thigh that progressed to both thighs over 5 years (Fig. 1A). On initial exam, the rash consisted of diffuse, erythematous macules with telangiectasia, lacking papules and Darier’s sign, resembling the rare disorder, TMEP. Skin biopsy revealed moderate infiltrate of mast cells in a perivascular and interstitial distribution associated with superficial telangiectasia confirming TMEP with D816V mutation in KIT in skin (Fig. 2A). Otherwise, all hematological and chemical laboratory values were within normal limits. PUVA, narrow band UV radiation, and 30 Gy in 10 fractions of electron beam radiotherapy were all ineffective. The rash progressed to her whole body including the abdomen, chest, arms, and face (Fig. 1C). In 2012, she developed abdominal pain and diarrhea. CT of abdomen and pelvis revealed new hepatosplenomegaly with ascites. Biopsy of colon revealed pan-colonic infiltration by mast cells. Bone marrow biopsy revealed a hypercellular marrow of >90% cellularity with 10–20% of cells found CD117 and CD25 positive atypical mast cells within multifocal clusters consistent with aggressive systemic mastocytosis (ASM) (Fig. 2C). Treatment with cladribine (a purine nucleoside analogue) then cabozantinib (a tyrosine kinase inhibitor of VEGF) improved the rash, but with unacceptable systemic toxicity. A repeat bone marrow biopsy contained over 35% mast cells. Despite two cycles of nivolumab (an immune checkpoint inhibitor of PD-1), her disease progressed and serum tryptase level rose to 60 ng/ml (Fig. 3).

She enrolled in clinical trial IRB 15-2178 using oral avapritinib (BLU-285, a targeted KIT inhibitor) 130 mg daily. Her rash and diarrhea resolved over 10 weeks (Figs 1B, D, and 2B) along with elevated serum tryptase level (Fig. 3), hepatosplenomegaly, and ascites. Bone marrow biopsy after two years of treatment revealed complete remission with a mildly elevated tryptase level.
Mastocytosis is a clonal hematopoietic stem cell disorder with mast cell expansion and accumulation. Most cases have an acquired driver mutation, somatic exon 17 KIT activating point mutation D816V (1). TMEP is an old terminology of a rare type of cutaneous mastocytosis (CM) that has a high frequency of progression to systemic disease, including ASM (2). TMEP is now reclassified under the term maculopapular cutaneous mastocytosis (MPCM) (3). To our knowledge, we describe the first and successful treatment of avapritinib for refractory MPCM in a 35-year-old woman who failed multiple lines of therapy. Within 8 weeks of treatment with avapritinib, her skin lesions resolved, and she achieved complete remission for over 3 years.

Current treatment for CM is oriented to reducing symptoms including antihistamines, cromoglycates, and anti-leukotrienes. Given the high risk of progression to devastating systemic diseases, CM, should be monitored for systemic involvement. Our patient met WHO criteria for ASM with major criteria of multifocal, dense infiltrates of mast cells aggregates detected in sections of bone marrow and extracutaneous organs of colon; minor criteria of D816V KIT mutation in bone marrow and skin, mast cells expressing both CD117 and CD25 in bone marrow, and serum tryptase level persistently over 20 ng/ml; C-findings of palpable hepatosplenomegaly and ascites.

If refractory to symptomatic therapy, in addition to workup for systemic involvement, patient with CM should be considered for systemic treatment targeting its driver mutation. Once the marrow is involved, minimal residual disease status should be monitored after initiation of systemic therapy, as it may be a predictor of relapse as seen in our case.

Avapritinib is a selective type I KIT D816V inhibitor. Type I inhibitors, unlike type II inhibitors binding to inactive kinase conformations, bind to the active conformation, leading to higher potency (4). Evans et al. (4) demonstrated superior efficacy compared to another type I inhibitor, dasatinib, and type II inhibitors (imatinib, sunitinib, regorafenib) both in vitro and in vivo. A phase 1 EXPLORER trial (NCT02561988) demonstrated decrease in bone marrow mast cells in advanced SM, as seen in our patient (5). Based on the promising results of phase 1 NAVIGATOR trial (NCT02508532), U.S. Food and Drug Administration has recently approved for its use in advanced gastrointestinal stromal tumor, another malignancy with acquired driver mutation of KIT/PDGFRA (6, 7). Common side effects are edema, anemia, and thrombocytopenia. Most reports are grade 1 or 2, and half of all patients reported greater than grade 3 without any discontinuation of the trial.

We report a successful and durable treatment of refractory CM, a debilitating mast cell disorder that has a high risk of progressing to systemic mastocytosis, that developed ASM. Our result raises consideration of additional treatment modality of refractory CM with systemic therapy, especially with targeted agents such as avapritinib.

REFERENCES

1. Erben P, Schwaab J, Metzgeroth G, Horny HP, Jawhar M, Sotlar K, et al. The KIT D816V expressed allele burden for diagnosis and disease monitoring of systemic mastocytosis. Ann Hematol 2014; 93: 81–88.
2. Severino M, Chandesris MO, Barete S, Tournier E, Sans B, Laurent C, et al. Telangiectasia macularis eruptiva perstans (TMEP): A form of cutaneous mastocytosis with potential systemic involvement. J Am Acad Dermatol 2016; 74: 885–891 e881.
3. Valient P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood 2017; 129: 1420–1427.
4. Evans EK, Gardino AK, Kim JI, Hodous BL, Shutes A, Davis A, et al. A precision therapy against cancers driven by KIT/ PDGFRA mutations. Sci Transl Med 2017; 9: eaao1690.
5. Drummond MW, DeAngelo DJ, Deininger MW, Radia D, Quiery AT, Hexner EO, et al. Preliminary safety and clinical activity in a Phase 1 study of Blu-285, a potent, highly-selective inhibitor of KIT D816V in advanced systemic mastocytosis (SM). Blood 2016; 128: 477–477.
6. Heinrich MC, Jones RL, Mehren Mv, Bauer S, Kang Y-K, Schofski P, et al. Clinical activity of avapritinib in ≥ fourth-line (4L+) and PDGFRA Exon 18 gastrointestinal stromal tumors (GIST). J Clin Oncol 2019; 37: 11022–11022.
7. Heinrich MC, Jones RL, von Mehren M, Schöfski P, Serrano C, Kang YK, et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumor (NAVIGATOR): a multicentre, open-label, phase 1 trial. Lancet Oncol 2020; 21: 935–946.