A Case of Indolent Systemic Mastocytosis Responding to Treatment with Avapritinib

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Introduction:

Systemic Mastocytosis (SM) is a rare disorder in which mast cells pathologically accumulate within tissue. The mast cells can be limited to the skin, or they can be systemic and involve extracutaneous tissues. One subtype of systemic mastocytosis (SM) is called indolent systemic mastocytosis, which is considered a less aggressive form of the disease, compared to advanced systemic mastocytosis which is considered to have organ impairment due to mast cell infiltration. Multi-kinase inhibitors such as Midostaurin and Imatinib are often used in the treatment of advanced SM or indolent SM that is refractory to conservative symptomatic treatment, but currently Avapritinib is reserved for treatment of advanced SM. Here is a case of an indolent SM responding to treatment with lower dose Avapritinib.

Case Description:

A 51 year old female was diagnosed with indolent systemic mastocytosis (SM) in 2013. She had vague ongoing symptoms including flushing, itching, telangiectasias, hives, and bloating for over ten years. Other issues, such as nasal congestion, rhinorrhea, cough, and wheezing, had been going on since childhood. The triggers, such as heat, friction, and diet, were often variable as well. These symptoms were occasionally relieved with Cetirizine. On 4/2013, a skin biopsy revealed telangiectasia macularis eruptive perstans, and results were positive for c-kit and tryptase. Bone marrow biopsy from 7/10/2013 revealed atypical mast cells with spindle morphology, as well as CD117, CD25, CD2 positivity. KIT D816V mutation was negative on the bone marrow biopsy. As she continued to have symptoms of diarrhea, itchiness, hives, and headaches, Cromolyn, Hydroxyzine, and injectable Omalizumab were started. Injectable epinephrine for possible anaphylaxis was also provided, but the patient never had an anaphylactic episode. Although some of the symptoms were controlled, other gastrointestinal symptoms including the bloating and diarrhea persisted. Given that her symptoms were still not optimally controlled, the patient was started on Imatinib in 2015, which improved the symptoms of SM. However, this caused significant transaminitis so Imatinib was discontinued. Midostaurin was then prescribed but the medication caused rashes, hepatotoxicity, and nausea so it was discontinued on 12/2018. In 2019, the patient's serum KIT mutation was found to be positive. She was then enrolled in an expanded access clinical trial. At the time, Avapritinib 200mg daily was used to treat aggressive SM, but the dosage was not yet established for indolent SM. Because there was hepatotoxicity to other tyrosine kinase inhibitors, the patient was started on a decreased dose of Avapritinib at 100mg daily on 4/2020. Over time there were three subsequent dose reductions of Avapritinib as the patient had gastrointestinal adverse events and because the indolent SM trials were done at 25mg daily. In 8/2020, Avapritinib was decreased from 100mg daily to 100mg every other day when she was having nausea, mental fog, and burning tongue ulcers. The mental fog resolved at this lowered dose and the gastrointestinal distress was improved but ongoing. There was also occasional skin flushing and nausea which was improved with the medication. In 3/2021, the dosage was adjusted to 75mg daily since the patient was able to tolerate it well for a few months. In 7/2021, she developed Covid-19 infection as well as neck, shoulder, and chest

pain so she stopped the medication completely for several weeks. The medication was resumed at 25mg daily after her recovery from the infection and musculoskeletal pain. Avapritinib 25 mg daily has since been controlling the patient's serum tryptase levels, itchiness, and gastrointestinal symptoms very well with no toxicities to the medication. Currently the patient still takes Famotidine, Cromolyn and Hydroxyzine. She only occasionally takes Ondansetron prophylactically, and she has stopped taking Pantoprazole completely.

Discussion:

Systemic mastocytosis is a rare disease which can be difficult to diagnose and stage, as seen in this patient who experienced symptoms for ten years before the official diagnosis was made. Although the bone marrow biopsy performed in 2013 was negative for KIT D816V mutation, this was likely a false negative as the assessment for that mutation was less sensitive at the time. For patients with indolent SM, treatment often involves symptom control. In this case, the patient was appropriately on an antihistamine, Cromolyn, and Omalizumab to decrease symptoms of mast cell overactivation. Despite more conservative treatment, she was still symptomatic, and treatment with other standard therapies for uncontrolled SM including imatinib and Midostaurin have been limited by transaminitis. Fortunately, she was able to tolerate Avapritinib. As of 2021 this medication has been approved by the US FDA for treatment of advanced SM. While Avapritinib has already been approved to treat aggressive SM, research is still being done on its use for indolent SM. For this patient, the oral multikinase inhibitor is highly effective against indolent SM, both in improving quality of life, decreasing symptoms, and effectively controlling serum tryptase levels. The dosage of 25mg daily of Avapritinib appears to be the ideal dosage for this patient, which also happens to be the same dose that is being studied in the PIONEER study that is investigating the safety and efficacy of avapritinib in patients with ISM with moderate-severe symptoms. Perhaps Avapritinib should be approved for use against the indolent form of systemic mastocytosis and not limited to the advanced type.

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