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Positive Quality Intervention: Avapritinib (Ayvakit®) for Indolent Systemic Mastocytosis

Description: This PQI will discuss the use of oral avapritinib in patients with indolent systemic mastocytosis (ISM).

Background: Avapritinib is a highly selective and potent tyrosine kinase inhibitor (TKI) that blocks D816V-mutated *KIT* and D842V platelet-derived growth factor receptor alpha (PDGFRA), which are mutations that confer resistance to other kinase inhibitors.[1,2] These mutations drive ISM, which is a clonal disease caused by mast cell activation, proliferation, and accumulation.[2] The KIT D816V mutation is the driver in approximately 95% of systemic mastocytosis (SM) cases. To establish a diagnosis of ISM, the criteria for systemic mastocytosis must be met; however, patients must not exhibit C-findings or an associated hematologic neoplasm. Additionally, patients typically have skin lesions and a low mast cell burden.[3,4] It is also important to distinguish ISM from Advanced SM, which includes Aggressive SM, SM-AHN, and Mast Cell Leukemia. The main complication with ISM is decreased quality of life due to uncontrolled, debilitating symptoms. Avapritinib previously received approval for adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a PDGFRA exon 18 mutation in 2020 and advanced systemic mastocytosis (AdvSM) in 2021. Avapritinib was approved in 2023 for the treatment of patients with ISM, and is the first and only FDA-approved medication for this indication.[1,5] This approval was based on the phase 2, randomized, placebo-controlled, double-blind PIONEER trial.[2] Adult patients with ISM and moderate to severe symptoms (total symptom score [TSS] $\geq$ 28; scores range from 0 to 110, with higher numbers indicating greater symptom severity) uncontrolled by at least two best supportive care (BSC) treatment agents were included. Two hundred twelve patients were randomly assigned (2:1) to receive avapritinib 25 mg once daily (n=141) or placebo (n=71), in addition to BSC. Overall, the median number of BSC treatment agents was 3 and about 12% and 7% of patients received prior cytoreductive or TKI therapy, respectively. The primary endpoint was mean change in TSS from baseline to week 24 in the intention-to-treat population. The mean decrease in TSS was 15.6 points in the avapritinib group compared to 9.2 points in the placebo group (P=0.003). Key secondary endpoints included $\geq$30% and $\geq$50% reduction in TSS, which indicate clinically important treatment responses. From baseline to week 24, 45% vs. 30% (P=0.009) of patients in the avapritinib and placebo groups, respectively, had a $\geq$30% reduction in TSS. During this same time period, 25% vs. 10% (P=0.005) of patients in the avapritinib and placebo groups, respectively, had a $\geq$50% reduction in TSS. Overall, avapritinib was well-tolerated with 21% of patients in both groups experiencing grade $\geq$3 adverse events (AEs) and 2% discontinuing treatment due to AEs in the avapritinib group compared to 1% in the placebo group. The most common AEs occurring at least two times that of placebo, not thought to be related to ISM, were flushing, edema (peripheral, face, and periorbital), increased alkaline phosphatase, and insomnia.

PQI Process:[1-3] Upon receiving a prescription for avapritinib:

- Confirm diagnosis for ISM
- Avapritinib is not recommended for the treatment of patients with platelet counts of < 50,000/mm^3
- Assess drug-drug interactions
    - Avoid concomitant use of strong or moderate CYP3A inhibitors or inducers
- Verify correct dose: 25 mg orally once daily (Note: Dosing varies for GIST and AdvSM indications)
    - Administer avapritinib on an empty stomach, at least 1 hour before or 2 hours after a meal
    - No dose modifications are recommended for adverse reactions
    - Dose modifications for renal impairment
        - No dose adjustment is recommended for patients with mild to moderate renal

impairment (creatinine clearance 30-89 mL/min)
        - Not studied in patients with creatinine clearance < 30 mL/min
    - Dose modifications for hepatic impairment
        - No dose adjustment is recommended for patients with mild to moderate hepatic impairment
        - Severe hepatic impairment (Child-Pugh Class C): 25 mg orally every other day
- Avapritinib is associated with moderate to high emetic risk, however, the incidence appears to be dose-dependent, as incidence is lower in the treatment of ISM (13%) compared to the treatment of AdvSM (24%) and GIST (64%)
    - Consider use of an antiemetic to be given as needed for nausea/vomiting
- No specific laboratory parameter monitoring is recommended for treatment of patients with ISM

Patient-Centered Activities:[1,2]

- Provide Oral Chemotherapy Education Sheet
    - Administer avapritinib on an empty stomach, at least 1 hour before or 2 hours after a meal
    - Do not make up for a missed dose within 8 hours of the next scheduled dose
    - Do not repeat dose if vomiting occurs after avapritinib administration but continue with next scheduled dose
- Counsel patients on potential drug-drug and drug-food interactions
- Discuss the most common AEs: headache, nausea, dizziness, diarrhea, flushing, edema (peripheral, face, periorbital), and insomnia
- Educate the patient on the risk of photosensitivity reactions, importance of limiting ultraviolet exposure during treatment, and using proper protection
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. AYVAKIT® (avapritinib) [prescribing information].
2. Gotlib J, Castells M, Oude Elberink H, et al. Avapritinib versus placebo in indolent systemic mastocytosis. *NEJM Evid.* 2023;2(6).
3. National Comprehensive Cancer Network. (Version 1.2023). Retrieved May 25, 2023, from https://www.nccn.org/professionals/physician_gls/pdf/mastocytosis.pdf.
4. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20): 2391-2405.
5. FDA approves Ayvakit (avapritinib) as the first and only treatment for indolent systemic mastocytosis. News release. Blueprint Medicines Corporation. May 22, 2023. Accessed May 25, 2023. https://ir.blueprintmedicines.com/news-releases/news-release-details/fda-approves-ayvakitr-avapritinib-first-and-only-treatment.