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

Description: This PQI will discuss the initiation and management of patients receiving avapritinib for Advanced Systemic Mastocytosis (AdvSM).

Background: Avapritinib is a potent tyrosine kinase inhibitor that targets platelet-derived growth factor receptor alpha (PDGFRA) and KIT exon mutants. KIT D816V mutation is expressed in 90-95% of patients with AdvSM, and results in autophosphorylation and increased survival of neoplastic mast cells. Avapritinib selectively targets and inhibits the autophosphorylation of KIT D816V mutation. Initially approved for the treatment of unresectable and metastatic gastrointestinal stromal tumor (GIST) harboring PDGFRA mutations, avapritinib was approved in 2021 for adult patients with AdvSM (including aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL)). Avapritinib was approved for AdvSM based on a phase I EXPLORER trial, and a phase 2 PATHFINDER trial which included adult patients with AdvSM (including ASM, SM-AHN, MCL) or relapsed/refractory myeloid malignancies. Fifty-three patients were evaluable for response across the two trials, 47% of patients had prior midostaurin use and 40% had ongoing corticosteroid use. The overall response rate (ORR) was 57% which included 28% of patients who had complete response (CR) or CR with partial recovery of peripheral blood counts. The ORR was 72.2% in treatment-naïve patients and 48.6% in patients with prior antineoplastic therapy including midostaurin. Median time to response was 2.1 months, and median duration of response was 38.3 months (95% CI: 19 months - not estimable). In the EXPLORER trial, non-traumatic intracranial hemorrhage (ICH) occurred in 8% of all patients, and in 44% of patients with platelets < 50 x 109/L. Considering this, patients with platelets < 50 x 10^9/L were excluded from the PATHFINDER trial. Safety was evaluated in 131 patients in both trials including 80 patients who received the starting dose of 200 mg daily. The most common non-hematological adverse events (incidence >20%) included periorbital edema, peripheral edema, diarrhea, nausea, and fatigue. The most common grade 3 toxicities included anemia, thrombocytopenia, and neutropenia. Dose interruption occurred in 60% of patients and 68% patients required a dose reduction. Among the 749 patients that received avapritinib, ICH occurred in 2.9% of patients; with <1% experiencing a serious ICH. Cognitive effects including memory impairment, cognitive disorder, confusion, delirium, and disorientation occurred in 39% of patients (3% ≥ Grade 3).

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

- Confirm diagnosis for AdvSM (**Advanced Systemic Mastocytosis Patient Diagnostic Algorithm** PQI)
- Avapritinib is not recommended in patients with platelet counts of < 50,000/mm^3
- Verify AdvSM dose: 200 mg orally once daily (Note: GIST dosing 300 mg orally once daily)
    - Dose should be taken on an empty stomach (1-hr prior or 2-hr after a meal)
    - Dose modifications for toxicity in AdvSM patients

First Dose Reduction	100 mg once daily
Second Dose Reduction	50 mg once daily
Third Dose Reduction	25 mg once daily
Fourth Dose Reduction	Permanently discontinue

- Assess drug-drug interactions
    - Avoid avapritinib administration with moderate or strong CYP3A4 inhibitors or inducers
        - If concomitant is unavoidable, reduce starting dose to avapritinib 50 mg once daily
- Monitor platelet counts every 2 weeks for the first 8 weeks

    - After 8 weeks, frequency of monitoring is dependent on the platelet count at that time:
        - Platelets < 75,000/mm^3: monitor every 2 weeks
        - Platelets 75,000 – 100,000/mm^3: monitor every 4 weeks
        - Platelets >100,000/mm^3: monitor as clinically indicated
- Dose modification for renal impairment
    - No dose adjustment is recommended for patients with mild to moderate renal impairment
    - Not studied in patients with creatinine clearance < 30 mL/min
- Dose modification for hepatic impairment
    - No dose adjustment is recommended for patients with mild to moderate hepatic impairment
    - Not studied in patients with total bilirubin > 3 times ULN
- Dose modifications for specific adverse reactions:

Adverse Effect	Grade	Recommendation
Intracranial Hemorrhage	Any Grade	Permanently discontinue
Central Nervous System Effects	Grade 1	Continue avapritinib, reduce dose or hold treatment until improvement to baseline or resolution of symptoms Resume at same or reduced dose
	Grade 2/3	Hold avapritinib until improvement to baseline/Grade 1/resolution Resume at same or reduced dose
	Grade 4	Permanently discontinue
Thrombocytopenia (platelet < 50,000/mm^3)		Hold avapritinib until resolution (platelet > 50,000/mm^3) Resume avapritinib at reduced dose Consider platelet support if platelet counts do not recover
Other Adverse Reactions	Grade 3/4	Hold until improvement to > Grade 2 Resume at same or reduced dose as clinically appropriate

Patient-Centered Activities:

- Provide Oral Chemotherapy Education Sheet
    - Avapritinib should be taken on an empty stomach, at least 1-hr prior to 2-hr after a meal
    - Do not make up for a missed dose within 8 hours of the next scheduled dose or if vomiting occurs
- Counsel patients on potential drug-drug and drug-food interactions including herbals and grapefruit juice
- Monitor patient for most common adverse effects
    - Central nervous side effects such as dizziness, trouble sleeping, changes in mood or behavior or any neurological sign or symptom related to intracranial hemorrhage
        - Report cognitive changes such as memory loss, forgetfulness, and confusion
    - Other common side effects include edema, fatigue, diarrhea, nausea, vomiting
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. AYVAKIT® (avapritinib) [prescribing information].
2. Gotlib J, Radia D, George T. Pure Pathologic Response Is Associated with Improved Overall Survival in Patients with Advanced Systemic Mastocytosis Receiving Avapritinib in the Phase I EXPLORER Study *Blood* (2020) 136 (Supplement 1): 37–38.
3. DeAngelo DJ, Reiter A, Radia D, et al. CT023 – PATHFINDER: Interim analysis of avapritinib (ava) in patients (pts) with advanced systemic mastocytosis (AdvSM). Abstract #CT023. Presented at the 2021 American Association for Cancer Research Annual Meeting, April 11, 2021.