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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.

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 advanced systemic mastocytosis, 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 June 2021 for adult patients with advanced systemic mastocytosis (AdvSM), a category that includes 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 (CRh). The ORR was 72.2% (95% CI 46.5-90.3%) in treatment-naïve patients (n=18) and 48.6% (95%CI 34.1-66^%) in patients with prior antineoplastic therapy including midostaurin (n=35). 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 bleeding (ICB) occurred in 8% of all patients, and in 44% of patients with platelets < 50 x 10^9/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, intracranial hemorrhage (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% being grade 3 or higher).

PQI Process: Upon receiving a prescription for avapritinib:

- Confirm diagnosis for AdvSM
- Avapritinib is not recommended for in patients with platelet counts of < 50,000/mm^3
- Verify dose – usual dose for AdvSM is 200 mg orally once daily which differs from usual dose for GIST which is 300 mg orally once daily
    - Dose should be taken on an empty stomach (1-hr prior or 2-hr after a meal)

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PQI Process Continued:

- Dose modifications for toxicity (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 use of avapritinib with a moderate CYP3A4 inhibitor is unavoidable, reduce starting dose to avapritinib 50 mg once daily
- Monitor Platelet Counts
  - Obtain platelet count every 2 weeks for the first 8 weeks
  - After 8 weeks, frequency of platelet count 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 < 30mL/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	Recommendation
Intracranial Hemorrhage	Any Grade • Permanently discontinue
Central Nervous System Effects (memory impairment, cognitive disorder, confusion, disturbances in attention, amnesia, mental impairment, mental status changes, dementia, abnormal thinking, mental disorder, and retrograde amnesia)	Grade 1 • Continue avapritinib, reduce dose or withhold treatment until improvement to baseline or resolution of symptoms • Resume at same or reduced dose
	Grade 2 • Hold avapritinib until improvement to baseline, Grade 1 or resolution of symptoms • Resume at same or reduced dose
	Grade 2 or 3 • Hold avapritinib until improvement to baseline, Grade 1 or resolution of symptoms

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	• Resume at same or reduced dose Grade 4 • Permanently discontinue
Thrombocytopenia (platelet < 50,000/mm3)	• Hold avapritinib until resolution (platelet > 50,000/mm^3) • Resume avapritinib at reduced dose • Consider platelet support if platelet counts do not recover (platelet > 50,000/mm^3)
Other Grade 3 or 4 Reactions	• Hold until improvement to > Grade 2 • Resume at same or reduced dose as clinically appropriate

Patient Centered Activities:

- Provide Oral Chemotherapy Education Sheet
- Counsel patient on proper medication administration
  - Avapritinib should be taken on an empty stomach, at least 1-hr prior to 2-hr after a meal
  - Missed dose can be taken within 8-hours of next scheduled dose
- Do not repeat dose if vomiting occurs after avapritinib administration
- 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
    - Patient and caregiver should be alert for cognitive changes such as memory loss, forgetfulness, and confusion
  - Other common side effects include edema, fatigue, diarrhea, nausea, vomiting

Supplemental Information:

- Patient Support Program: YourBlueprint
  - Dedicated case manager available at 1-888-258-7768 (1-888-BLUPRNT)
  - Monday – Friday 8AM – 8PM ET
- Co-Pay Assistance Program
  - Eligible, commercially insured patients may reduce their out-of-pocket costs ($0 per month)

References:

1. AYVAKIT® (avapritinib) [prescribing information]. Cambridge, MA: Blueprint Medicines Corporation; June 2021.
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.