Positive Quality Intervention: Gilteritinib (Xospata®) for Relapsed/Refractory Acute Myeloid Leukemia

Description: This PQI will discuss proper patient selection and management of adverse events related to the administration of oral gilteritinib pharmacotherapy in patients with relapsed/refractory (R/R) acute myeloid leukemia (AML) that have an FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test. Optimal patient identification, dosing, and follow-up are essential to help patients fully benefit from this medication.

Background: Gilteritinib is a tyrosine kinase inhibitor (TKI) that has demonstrated activity in patients with R/R AML who have mutations in the internal tandem duplication and/or tyrosine kinase domain of FLT3 (found in 30% of AML population).1 This represents a treatment paradigm shift as the first oral monotherapy option for this particular subset of FLT3 mutation positive AML patients who, if interested in further treatment, would traditionally utilize IV salvage chemotherapy. Clinicians should be aware of the need for molecular testing and identifying therapy options with the highest level of evidence. NCCN Guidelines highly recommends (Category 1) gilteritinib for both fit and unfit R/R FLT3 AML patient with prior TKI use.2 In the final analysis of the ADMIRAL study, overall survival was reported as 9.3 months for patients receiving gilteritinib versus 5.6 months for those receiving salvage chemotherapy (Hazard Ratio = 0.64 (95% CI 0.49, 0.83), P=0.0004).3 The rate of complete response was reported at 22.6%. The median time to first response was 2 months and transfusion-independence was observed in 34.5% of patients, representing a potential improvement in quality of life. Gilteritinib is actively being studied in other AML settings including front-line therapy with induction chemotherapy, maintenance therapy after transplant, and in combination with hypomethylators.

PQI Process:1 Upon receipt of new prescription for gilteritinib:
- Verify genetic testing is complete with positive FLT3 mutations and appropriate prior lines of therapy
- Ensure that the correct dose is prescribed (three 40 mg oral tablets (120 mg total)) by mouth daily
- Verify that baseline blood counts, chemistries, as well as creatine phosphokinase (CPK) have been assessed prior to initiation of gilteritinib
  - Schedule these labs for every week for the first month, every other week for the second month, and once monthly thereafter for the duration of therapy
- Ensure ECG results obtained prior to initiation, on days 8 and 15 of the first cycle, and consider for the next two cycles
- Monitor for any signs/symptoms of pancreatitis, posterior reversible encephalopathy syndrome (PRES), differentiation syndrome
  - Fever, dyspnea, hypoxia, pulmonary infiltrates, pleural effusions, edema
- Dosage modifications as described in Table in Supplemental Information
- Important: Upon refill, check and clarify dosing, quantity, and instructions to the patient (number of tablets per dose, etc.)

Patient-Centered Activities:1
- Provide Oral Chemotherapy Education (OCE) sheet
- Educate patient on dosing and schedule: 120 mg (3 x 40 mg oral tablets) once daily continuously
- Ensure patient knows that the drug may be taken without regard to meals and that the tablets should not be broken or crushed

IMPORTANT NOTICE: NCODA has developed this Positive Quality Intervention platform. This platform is intended as an educational aid, does not provide individual medical advice, and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication. The materials contained in this platform do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA. NCODA does not ensure the accuracy of the information presented and assumes no liability relating to its accuracy. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional. It is the individual’s sole responsibility to seek guidance from a qualified healthcare professional. Updated 10.2.23
• If dose is missed, take as soon as possible if at least 12 hours before next scheduled dose *do not take two doses within 12 hours*
• Counsel female patients of childbearing age to use effective contraception during treatment and for at least six months after the last dose of gilteritinib; male patients should utilize contraception during treatment and for at least 4 months after the last dose of gilteritinib
• Educate patient to call office at first sign of fever (>100.4°F)
• Consider the use of antidiarrheals
• Patient Assistance: NCODA Financial Assistance Tool

References:
1. XOSPATA® (gilteritinib) [package insert].

Supplemental Information:
Dose Modifications

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<thead>
<tr>
<th>Adverse Event</th>
<th>Recommended Action</th>
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<tbody>
<tr>
<td>Differentiation Syndrome</td>
<td>Systemic steroids until resolved for 3 days (hold if signs remain &gt; 48 hr); resume when symptoms improve to Grade 2</td>
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<tr>
<td>PRES</td>
<td>Discontinue gilteritinib</td>
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<tr>
<td>QTc interval &gt; 500 msec</td>
<td>Interrupt gilteritinib and resume at reduced dose of 80 mg daily when QTc interval returns within 30 msec of baseline or ≤480 msec</td>
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<td>QTc interval increased by &gt; 30 msec on ECG on day 8 of cycle 1</td>
<td>If confirmed on day 9, consider dose reduction to 80 mg daily</td>
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<td>Pancreatitis</td>
<td>Hold until resolved and resume at a reduced dose of 80 mg daily</td>
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<tr>
<td>Other Grade 3 or higher toxicity</td>
<td>Hold until toxicity resolves or improves to Grade 1 and reduce dose to 80 mg daily</td>
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Common adverse events (all grade >30%)
• Transaminase increase (51%)
• Fatigue/malaise (44%)
• Fever (41%)
• Mucositis (41%)
• Edema (40%)
• Rash (36%)
• Diarrhea (35%)
• Dyspnea (35%)
• Nausea (30%)

Rare and serious adverse events
• Electrocardiogram QT prolonged (9%)
• Hypersensitivity (8%)
• Pancreatitis (5%)
• Cardiac failure (4%)
• Pericardial effusion (4%)
• Differentiation syndrome (3%) [Boxed Warning]
• PRES (1%)