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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 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 benefit fully while taking this medication.

Background: Gilteritinib is a tyrosine kinase inhibitor that has demonstrated activity in patients with relapsed/refractory (R/R) AML who have mutations in the internal tandem duplication (ITD) and/or tyrosine kinase domain (TKD) of FLT3 (found in 30% of AML population). This represents a treatment paradigm shift as the *first oral monotherapy option* for this particular subset of FLT3- mutated 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. In the final analysis of the ADMIRAL study, Overall Survival (OS) 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). The rate of complete response (CR/CRh) 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: Upon receipt of new prescription for gilteritinib:

- Verify genetic testing is complete with positive FLT3 mutation and appropriate prior lines of therapy
- Ensure that the correct dose is prescribed (3 x 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 of gilteritinib as well as appointments scheduled to receive follow-up ECGs on days 8 and 15 of the first cycle and consider for the next two cycles
- Monitor for any signs/symptoms of pancreatitis, PRES, differentiation syndrome
    - Fever, dyspnea, hypoxia, pulmonary infiltrates, pleural effusions, edema
- Call office at first sign of fever (temperature >100.4F)
- Consider the use of antidiarrheals
- Important: Upon refill, check and clarify dosing, quantity, and instructions to the patient (number of tablets per dose, etc.)

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Patient Centered Activities:

- Provide Oncology Chemotherapy Education (OCE) sheet
- Ensure patient knows the appropriate drug dose and schedule (3 x 40 mg oral tablets)120 mg total) 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
- Patients should take their dose as soon as possible if missed on the same day if at least 12 hours before next scheduled dose followed by a return to normal dosing schedule *Patient should 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
- Dosage modifications as described in Table in *Supplemental Information*

References:

1. XOSPATA® (gilteritinib) [package insert].
2. Perl AE, Altman JK, Cortes J, et al. Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicenter, first-in-human, open-label, phase 1-2 study. *Lancet Oncology*. 2017;18(8):1061-1075.
3. Usuki K, Sakura T, Kobayashi Y, et al. Clinical profile of gilteritinib in Japanese patients with relapsed/refractory acute myeloid leukemia: an open-label phase 1 study. *Cancer Science*. 2018;109(10):3235-3244.
4. Perl AE, Cortes JE, Strickland SA, et al. An open-label, randomized phase III study of gilteritinib versus salvage chemotherapy in relapsed or refractory FLT3 mutation- positive acute myeloid leukemia. *Journal of Clinical Oncology*. DOI: 10.1200/JCO.2017.35.15_suppl.TPS7067.

Supplemental Information

Dose Modifications

Adverse Event	Recommended Action
• Differentiation Syndrome	•Systemic steroids until resolved for 3 days (interrupt gilteritinib if signs remain >48H) •Resume when symptoms improve to Grade 2
• Posterior reversible encephalopathy syndrome (PRES)	•Discontinue gilteritinib
• QTc interval > 500 msec	•Interrupt gilteritinib and resume at reduced dose of 80 mg (2 x 40 mg tablets) daily when QTc interval returns within 30 msec of baseline or ≤480 msec
• QTc interval increased by > 30 msec on ECG on day 8 of cycle 1	•Confirm with ECG on day 9 •If confirmed, consider gilteritinib dose reduction to 80 mg (2 x 40 mg tablets) daily
• Pancreatitis	•Interrupt gilteritinib until pancreatitis is resolved and resume at a reduced dose of 80 mg (2 x 40 mg tablets) daily
• Other grade 3 or higher toxicity (related to treatment)	•Interrupt gilteritinib until toxicity resolves or improves to grade 1 and reduce dose to 80 mg (2 x 40 mg tablets) daily

Co-Pay Assistance

- Patients with commercial paying insurance are eligible for co-pay support
  - Patients pay as little as $0 per prescription
  - Enrollment is for a 12 month period and the program benefit covers up to a maximum of $25,000 per calendar year
  - Contact XOSPATA® support solutions (1-844-632-9272) OR your preferred network specialty

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]
- Posterior reversible encephalopathy syndrome (1%)

*AE reported from 319 gilteritinib patients across 3 clinical trials