National Community Oncology Dispensing Association, Inc.
PASSION FOR PATIENTS

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Positive Quality Intervention: Copanlisib for the Management of Relapsed/Refractory Follicular Lymphoma

Description:

There are a number of treatment options for patients with follicular lymphoma that has relapsed or is refractory to first line options. In September 2017, the FDA approved copanlisib for the treatment of adults who have received at least two other previous therapies.

Background:

Non-Hodgkin's lymphoma includes a variety of both aggressive and indolent malignancies. Follicular lymphoma is the most common subtype of indolent Non-Hodgkin's Lymphoma.
Select treatment options include:

- Cyclophosphamide, vincristine, prednisone (CVP) + obinutuzumab or rituximab
- Rituximab
- Lenalidomide +/- rituximab
- Ibritumomab tiuxetan
- Idelalisib (refractory to alkylator and rituximab)
- Copanlisib (refractory to two prior therapies)
- Duvelisib (refractory to two prior therapies)

Copanlisib is an intravenous phosphatidylinositol 3-kinase (PI3K) inhibitor. PI3K pathways are often hyperactive in B-Cell malignancies. The first FDA approved PI3K inhibitor for follicular lymphoma was idelalisib which is efficacious but is associated with potentially serious toxicities including hepatic dysfunction, colitis, autoimmune toxicity, and pneumonitis. A phase II study demonstrated an objective response rate of 43.8% with copanlisib. The most common treatment related adverse events were hyperglycemia (59.5%), hypertension (54.8%), fatigue (48.8%) and diarrhea (40.5%). Grade 3+ adverse events were observed in 31%, 4.8% and 11.9% of patients, respectively. The most common grade 3+ adverse events were lung infection (10.7%), diarrhea (3.6%) and febrile neutropenia (3.6%).

PQI Process:

Upon receipt of an order for copanlisib:

- Ensure patient is an appropriate candidate for copanlisib and has received at least two prior therapies
- Discuss potential risks of copanlisib therapy
  - Increased risk of infection
    - Monitor for signs and symptoms of infection, including *pneumocystis jirovecii* pneumonia (PJP)
    - For suspected PJP infection of any grade: Withhold copanlisib; if infection is confirmed, treat infection until resolution, then resume copanlisib at previous dose with concomitant PJP prophylaxis.
  - Hyperglycemia
    - Monitor blood glucose at least pre- and post-dose. It may be necessary to monitor more frequently as clinically indicated
    - Grade 3 or 4 hyperglycemia has occurred in >25% of patients. In clinical trials, copanlisib induced hyperglycemia peaked 5-8 hours post-infusion and returned to baseline within 24 hours

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        - Pre-dose fasting blood glucose ≥160 mg/dL or random (non-fasting) blood glucose ≥200 mg/dL:
            - Withhold copanlisib until fasting glucose is ≤160 mg/dL or a random (non-fasting) blood glucose is ≤200 mg/dL.
        - Pre-dose or post-dose blood glucose ≥500 mg/dL:
            - First occurrence: Withhold copanlisib until fasting blood glucose is ≤160 mg/dL, or a random (non-fasting) blood glucose is ≤200 mg/dL. Reduce dose from 60 mg to 45 mg.
            - Subsequent occurrences: Withhold copanlisib until fasting blood glucose is ≤160 mg/dL, or a random (non-fasting) blood glucose is ≤200 mg/dL. Reduce dose from 45 mg to 30 mg. If hyperglycemia is persistent at the 30 mg dose, discontinue copanlisib.

    - Hypertension
        - Monitor blood pressure at least pre- and post-dose. It may be necessary to monitor more frequently as clinically indicated
        - Transient hypertension was observed in clinical trials in ~30% of patients but was not a significant cause of treatment delay
        - In clinical trials, blood pressure remained elevated 6-8 hours post infusion
        - Potential intervention:
            - For pre-dose elevation: withhold copanlisib until blood pressure is <150/90 (both systolic and diastolic) based on 2 consecutive measurements at least 15 minutes apart
            - For post-dose elevation: If elevation in blood pressure is life threatening, discontinue copanlisib. If antihypertensive therapy is not required, continue copanlisib at the previous dose. If antihypertensive treatment is necessary, consider copanlisib dose reduction from 60 mg to 45 mg (or from 45 mg to 30 mg). Discontinue copanlisib if blood pressure remains uncontrolled (>150/90) despite appropriate antihypertensive treatment.
    - Drug-Drug Interactions
        - Copanlisib is a major substrate of CYP3A4
        - Avoid concomitant use of strong CYP3A4 inhibitors
            - Potential intervention: If concurrent therapy cannot be avoided, reduce the copanlisib dose to 45 mg

Patient Centered Activities:

- Educate patients on copanlisib therapy and recommend appropriate interventions:
    - Hyperglycemia
        - Monitor patients for signs of confusion, feeling sleepy, more thirst, more hunger, passing urine more often, flushing, fast breathing, or breath that smells like fruit
    - Hypertension
        - Monitor patients for signs/symptoms of high blood pressure like very bad headache or dizziness, passing out, or change in eyesight.

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- Diarrhea
  - Monitor for how many bowel movements occur each day. Recommend to patients to drink 8–10 glasses of water or fluid each day unless care provider has instructed to limit your fluid intake. Antidiarrheal medications be used to help control symptoms
- Allergic or cutaneous reactions
  - Monitor for signs of rash, hives, itching, red/swollen/blistered/peeling skin with/without fever, wheezing, tightness in the chest/throat, trouble breathing/swallowing/talking, unusual hoarseness, or swelling of the mouth/face/lips/tongue/throat
- Infections and pneumonitis
  - Monitor for any signs of lung or breathing problems like shortness of breath or other trouble breathing, fever, chills, very bad sore throat, ear or sinus pain, cough, more sputum or change in color of sputum, pain with passing urine, mouth sores, or wound that will not heal

References:

1. Dreyling M, et al. Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. *Annals of Oncology*. 2017; 28: 2169-78. doi:10.1093/annonc/mdx289
2. Aliqopa (copanlisib) [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc. 2017.