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Positive Quality Intervention: Copanlisib (Aliqopa®) Toxicity Management

Description: Copanlisib is an intravenous (IV) phosphatidylinositol 3-kinase (PI3K) inhibitor indicated for the treatment of relapsed follicular lymphoma (FL) in patients that have received at least two prior systemic therapies.[1] This PQI will review how to manage select toxicities associated with copanlisib.

Background: Copanlisib is a pan-class I PI3K inhibitor with preferential inhibitory activity against PI3K-α and PI3K-δ isoforms, which are expressed in malignant B-cells.[2] Accelerated approval of copanlisib was based on the results of a phase II trial in relapsed or refractory indolent B-cell lymphomas; overall response rate (ORR) of 59% and complete response (CR) rate of 12% were observed.[3] The adverse events associated with copanlisib can be explained by the PI3K isoform targets with the most common adverse events being hyperglycemia, hypertension, infections, and diarrhea.[1-3] Hyperglycemia is an expected on-target effect of PI3K-α inhibition with systemic inhibition of PI3K-α.[4] Blood glucose typically peaked 5 to 8 hours post-infusion with grade 3 or 4 hyperglycemia (blood glucose ≥ 250 mg/dL) occurring in 41% of patients treated with serious hyperglycemic events occurring in 2.8% of patients.[1] Hypertension associated with copanlisib peaks 2 hours post-infusion and resolves within 24 hours.[1] Grade 3 hypertension (≥160/100 mmHg) occurred in 26% of patients with serious hypertensive events occurring in 0.9% of patients.[1] Infections occurred in patients receiving copanlisib with 19% of patients experiencing serious infections.[1] Diarrhea has been commonly seen with various other PI3K-inhbitors and was also seen in copanlisib trials with diarrhea developing in 36% of patients with Grade 3 in 5% of patients.[1] There are currently no black box warnings and both hypertension and hyperglycemia were observed to be transient. Follicular lymphoma RR was 59%, CR was 20%, and ORR was 60%.[5] Below we will review the prevention and management of common toxicities associated with copanlisib including hyperglycemia, hypertension, infections, and diarrhea.

November 13, 2023 – Bayer announced it will work with the FDA on a voluntary withdrawal of the Aliqopa® (copanlisib) U.S. New Drug Application for adult patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies.

PQI Process:

- Hyperglycemia prevention and management:[1]
  - Check blood glucose prior to copanlisib infusion and withhold dose unless the following parameters have been met:
    - Fasting plasma glucose ≤ 160 mg/dL OR random glucose ≤ 200 mg/dL
    - If pre/post-dose blood glucose ≥ 500 mg/dL then withhold until above parameters have been met and reduce copanlisib from 60 mg to 45 mg
    - On subsequent occurrences, reduce to 30 mg when above parameters have been met
    - If persistent, discontinue
  - Nondiabetic patients:[4]
    - Consider checking HbA1c prior to copanlisib treatment and re-checking once treatment is discontinued
      - Patients who develop an increase in HbA1c during copanlisib treatment should be re-tested in 3 months to determine if HbA1c has returned to baseline
    - Post-infusion monitoring is not needed for nondiabetic patients
    - Insulin is discouraged in nondiabetic patients due to the increased risk of hypoglycemia

        - Encourage adequate hydration
    - Prediabetic/diabetic patients:[1,4]
        - Check HbA1c prior and consider consulting with an endocrinologist prior to treatment
        - Post-infusion blood glucose should be checked, and monitoring should occur
            - Post-dose blood glucose ≥ 500 mg/dL consider reduction to 45 mg with subsequent infusion
        - When a meal is consumed within 8 hours post-infusion ensure low carbohydrate diet
- Hypertension monitoring and management:
    - Check blood pressure at least 15 minutes prior infusion proceed if:
        - BP ≤ 150/90 mmHg
        - If anti-hypertensives were required, consider reducing to 45 mg
        - Discontinue if blood pressure remains uncontrolled despite anti-hypertensives
- Infection prevention and management:
    - Initiate prophylaxis for pneumocystis jirovecii pneumonia (PJP) prior to initiating treatment
    - Monitor patients for signs and symptoms of infection and withhold for Grade 3 or higher
- Neutropenia
    - Reported: All Grade (32%), Grade 3 (10%), Grade 4 (15%)[1]
    - Monitor blood counts at least weekly while under treatment
    - ANC <0.5 x 10^3 cells/mm^3 hold and monitor until ANC ≥0.5 x 10^3 cells/mm^3 then resume at previous dose
    - If ANC 0.5 x 10^3 cells/mm^3 or less recurs, then reduce to 45 mg
- Diarrhea management:
    - If diarrhea develops, encourage adequate hydration and counsel on eating several small meals a day while adhering to the BRAT diet
        - See **Oncolytic Induced Diarrhea** PQI
    - Consider use of over the counter (OTC) anti-diarrheal including loperamide
    - Grade 3 diarrhea, hold until diarrhea resolves to ≤ Grade 1 and consider reduction to 45 mg[4]

Patient-Centered Activities:

- Consider endocrinology consult in diabetic patients starting copanlisib
- Counsel all patients on signs and symptoms of hyperglycemia, encourage a low-carbohydrate diet and consider insulin dose adjustments in diabetic patients already on insulin 6-8 hours post infusion
- Check blood pressure at least 15 minutes prior to infusion and consider the use of anti-hypertensives if blood pressure ≥ 150/90 mmHg on two or more blood pressure checks
- Ensure high-risk patients are on PJP prophylaxis
- Counsel patient on use of OTC anti-diarrheal if diarrhea occurs

References:

1. Aliqopa® (copanlisib) [prescribing information].
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3. Dreyling M, Santoro A, Mollica L, et al. Phosphatidylinositol 3-kinase inhibition of copanlisib in relapsed or refractory indolent lymphoma. *J Clin Oncol.* 2017;35(35):3898-3905.
4. Cheson B, O'Brien S, Ewer M, et al. Optimal management of adverse events from copanlisib in the treatment of patients with non-hodgkin lymphomas. *Clin Lymphoma Myeloma Leuk.* 2019;19(3):135-141.
5. Dreyling M, Santoro A, Mollica L, et al. Long-term safety and efficacy of the PI3K inhibitor copanlisib in patients with relapsed or refractory indolent lymphoma: 2-year follow-up of the CHRONOS-1 study. Am J Hematol. 2020;1–10. https://doi.org/10.1002/ajh.25711.