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-inhibitors 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.

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-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
  - 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

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PQI Process continued:

- 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:
  - Before initiating initiate prophylaxis for pneumocystis jirovecii pneumonia (PJP)
  - 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 10³ cells/mm³ hold and monitor until ANC ≥0.5 x 10³ cells/mm³ then resume at previous dose
  - If ANC 0.5 x 10³ cells/mm³ 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 mg4

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

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References:


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