CLINICAL VIGNETTE

Alpelisib Induced Hyperglycemia

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A 59-year-old female presented to Endocrinology for evaluation and management of hyperglycemia. Her past medical history includes hypothyroidism, hyperlipidemia, atrial fibrillation, urinary tract infections, yeast infections, and metastatic breast cancer with diffuse bony metastases, which progressed on letrozole. Liquid Biopsy demonstrated phosphatidylinositol 3-kinase catalytic subunit alpha (PIK3CA) mutation positivity. She was started on alpelisib and fulvestrant for treatment of breast cancer and subsequently developed hyperglycemia. She had no prior history of diabetes. Prior to alpelisib, her fasting glucose ranged from 92-110 mg/dL. After starting alpelisib, her fasting glucose ranged from 130-208 mg/dL despite treatment with metformin 1000 mg twice daily. She reported multiple symptoms attributed to hyperglycemia including brain fog, fatigue, chronic pain, chronic weakness, diarrhea, urinary urgency, and dysuria. Physical examination was limited as the initial office visits were conducted via telehealth. She was well-appearing, and in no acute distress with a BMI 33 kg/m^2.

Prior to starting alpelisib, her HgbA1c was 4.9%. After starting alpelisib, her HgbA1c increased to 7.4%. A trial of pioglitazone did not significantly improve glucose values. Given her history of urinary tract infections and yeast infections, sodium-glucose cotransporter-2 (SGLT2) inhibitors were not initiated. Linagliptin was briefly added, however, resulted in hypoglycemia, and was subsequently stopped. Due to disease progression, alpelisib was discontinued and replaced by capecitabine. Her hyperglycemia normalized, and all diabetes medications were discontinued.

Discussion

Alpelisib is an α specific phosphatidylinositol 3-kinase (PI3K) inhibitor FDA indicated for use with fulvestrant in advanced or metastatic PIK3CA mutated hormone receptor-positive, human epidermal growth factor receptor 2 negative breast cancer. In SOLAR-1, alpelisib in combination with fulvestrant prolonged median progression-free survival to 11 months compared to 5.7 months in placebo-fulvestrant group, hazard ratio (HR), 0.65; 95% confidence interval (CI), 0.5–0.85; $p < 0.001$. The most common adverse effect was hyperglycemia, with 63% of the alpelisib-fulvestrant group patients experiencing hyperglycemia versus 9.8% of the placebo-fulvestrant group. In the alpelisib-fulvestrant group, 32.7% had blood sugars of 251-500 mg/dL, and 3.9% had blood sugars greater than 500 mg/dL, compared to 0.3% and 0.3%, respectively, in the placebo-fulvestrant group. Ultimately, 6.3% of the alpelisib-fulvestrant patients discontinued alpelisib due to hyperglycemia.[1]

Insulin regulates blood glucose through (1) inducing glucose uptake in the adipose tissue and skeletal muscle, and (2) promoting glycogen synthesis and decreasing glycogenolysis. Insulin's actions are mediated through PI3K. Hence, PI3K-α inhibition results in hyperglycemia, causing increased pancreatic insulin release. This hyperinsulinemia may impair the action of PI3K inhibition.[2]

Patients with pre-diabetes at baseline had a higher incidence of hyperglycemia. Enrollment criteria for the study initially included glycosylated hemoglobin <8.0%, which later changed to <6.5%. Median onset of hyperglycemia after initiating alpelisib was 15 days, and median time to improvement in hyperglycemia was 6 days.[3]

In SOLAR-1, first-line treatment for fasting hyperglycemia of 140-160 mg/dL was metformin. If hyperglycemia persisted, addition of pioglitazone was advised. If fasting plasma glucose remained higher than 161 mg/dL, alpelisib dose was decreased. For fasting plasma glucose greater than 251 mg/dL, metformin plus pioglitazone was initiated, and alpelisib was held until fasting plasma glucose was below 160 mg/dL. Insulin could be utilized for 1 to 2 days as a rescue measure. For fasting plasma glucose >500 mg/dL, alpelisib was held and endocrinology was consulted, in addition to starting metformin and pioglitazone.[3] Given insulin can stimulate the PI3K pathway, it should be reserved as last line therapy. Use of SGLT2 inhibitors for alpelisib-associated hyperglycemia inadequately managed with metformin with or without pioglitazone has been promising.[2,4] However, multiple cases of diabetic ketoacidosis (DKA) have been reported in patients on alpelisib without treatment with SGLT2 inhibitors, in patients with and without a prior diagnosis of diabetes. In these cases, insulin was initiated as rescue treatment. In the majority of these cases, patients returned to euglycemia with discontinuation of alpelisib.[5-9] Given the rare side effect of euglycemic DKA with SGLT2 inhibitors, patients should be aware to monitor for symptoms suggestive of DKA (nausea, vomiting, abdominal pain, fatigue, shortness of breath).[10]

Given alpelisib's mechanism of action, hyperglycemia is an on-target effect. Hyperglycemia was the most common side effect of alpelisib, and was severe enough to require treatment discontinuation in multiple patients. Metformin plus low carbo-

hydrate diet are first line. SGLT2i inhibitors and pioglitazone have been studied - glucagon-like peptide 1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and acarbose have also been recommended as second line agents.[3,11] Insulin and insulin secretagogues should be reserved for fasting hyperglycemia >250 mg/dL, given it may impair alpelisib's activity. Persistent hyperglycemia may require discontinuation of alpelisib. Normalization of glucose typically occurs within 1 week of discontinuation, as was seen in our patient.[2]

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