


S.U.G.A.R: A Case to Outline Tactics for the Prevention of Alpelisib-Induced Hyperglycemia

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Abstract

Postmenopausal patients with metastatic breast cancer (mBC) may live years with their disease on therapies with minimal toxicities but they will eventually progress on first-line therapy. For those eligible for second-line therapy, PIK3CA mutation testing is recommended in estrogen receptor–positive, her2-negative disease. If present, alpelisib, a PI3K inhibitor, has been shown to improve progression-free survival. Hyperglycemia is a common side effect of alpelisib. We describe a case of diabetic ketoacidosis (DKA) necessitating treatment in the intensive care unit (ICU) in a woman with type 2 diabetes mellitus (T2DM) started on alpelisib. A 76-year-old female with diet-controlled T2DM and mBC was placed on second-line treatment with alpelisib after progression on first-line therapy. After more than 2 weeks of treatment, the patient presented to the emergency department with nausea and vomiting. Lab results showed DKA and she was admitted to the ICU for further management. This case highlights the need for a multidisciplinary approach to caring for patients who are started on a PI3K inhibitor. We propose 5 guidelines to prevent hyperglycemia in those started on alpelisib: (1) strict criteria for initiating alpelisib, (2) understand the steps needed to prevent hyperglycemia, (3) get help from a multidisciplinary team, (4) act immediately when hyperglycemia is noted, and (5) record blood glucose values. By implementing these steps, we hope to prevent critical hyperglycemic episodes in vulnerable patients on alpelisib.

Keywords

hematology/oncology, breast cancer, pharmacology

Introduction

Postmenopausal women with metastatic estrogen receptor (ER)-positive and HER2-negative breast cancer will likely receive first-line therapy, which consists of palbociclib, ribociclib, or abemaciclib (CDK4/6 inhibitors), and endocrine therapy such as an aromatase inhibitor.¹ For those requiring second-line therapy, the National Comprehensive Cancer Network (NCCN) recommends testing for phosphatidylinositol-3 kinase catalytic subunit alpha (PIK3CA), mutation. If present, alpelisib, a PI3K inhibitor, should be utilized.²

Alpelisib was approved in May 2019 in combination with fulvestrant for women with ER-positive, HER2-negative metastatic breast cancer with a PIK3CA mutation after progression on first-line therapy.³ This approval was based on SOLAR-1, which was a randomized, placebo-controlled phase 3 trial which examined 572 patients.³ This study reported an improved median progression-free survival with alpelisib and fulvestrant, compared with fulvestrant alone (11 months vs 5.7 months, $P < .001$). Common side effects of alpelisib were found to be fatigue, weight loss, lymphopenia,

anemia, and hyperglycemia. In fact, most of the patients (63.7%) reported hyperglycemia, defined by the trial as a blood glucose value greater than 160 mg/dL. Of these patients, 51.4% reported grade 3 hyperglycemia (250–500 mg/dL) and 6% developed grade 4 hyperglycemia (>500 mg/dL). Hyperglycemic events were more common in those with metabolic dysregulation. Prediabetes (defined as having an A1c of 5.7%–6.4% and/or a fasting blood sugar of 100–126 mg/dL) and type 2 diabetes mellitus (T2DM; defined as having an A1c of 6.5% or above and/or a fasting blood sugar >126 mg/dL) are common metabolic disorders.⁴ As a result, the overlap between those with breast cancer and diabetes is

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commonly seen. In the SOLAR-1 trial, 56% of patients had prediabetes, whereas 4% had T2DM.³

Rarely, this medication can lead to life-threatening hyperglycemia crisis. In the SOLAR-1 trial, diabetic ketoacidosis (DKA) was reported in 0.4% of patients.³ In addition, there have been several case reports in the literature reporting on life-threatening DKA after the initiation of alpelisib.⁵⁻⁸

Here, we describe a case of DKA necessitating treatment in the intensive care unit (ICU) in a woman with type 2 diabetes managed with diet started on alpelisib. The purpose of this case report is 2-fold: First, we aim to highlight this life-threatening adverse reaction and bring awareness to the possibility of DKA induced by alpelisib. As women with breast cancer live longer and metabolic diseases become more prevalent in our society, those on alpelisib may be at risk of lethal hyperglycemia episodes. Second, we want to stress the importance of multidisciplinary approach and outline tactics using the acronym S.U.G.A.R for the prevention of critical hyperglycemia and DKA in patients with breast cancer who have prediabetes or T2DM on alpelisib.

Case Presentation

A 76-year-old female, originally diagnosed with breast cancer in 1990, developed metastatic disease in her liver, bones, and lung in 2019. At the time of progression, she was placed on first-line therapy with palbociclib and fulvestrant. Patient had 22 months of disease stability but developed disease progression in her liver. As such, molecular profiling on her tumor tissue was done and revealed a PIK3CA mutation. She was started on second-line treatment with alpelisib 300 mg/d.

Patient carried a medical history of T2DM. She had underlying T2DM, uncontrolled with an A1c 8%, managed on lifestyle modifications with diabetes diet. Due to concerns about the potential of the drug exacerbating her insulin resistance and causing hyperglycemia, she was counseled extensively on the risk of drug-induced hyperglycemia. Prior to alpelisib initiation, she was taught how to use a glucometer and counseled to use her primary care physician for further glucose monitoring.

Patient was contacted by her oncologist twice per week for 2 weeks after the initiation of alpelisib. During the first week, her self-reported random blood glucose levels were in the acceptable range (range: 89-145 mg/dL). The second week revealed fasting blood glucose levels between 110 and 162 mg/dL. After the fourth call on day 12 of therapy, she was told to call the clinic with any rising blood glucose values. After 14 days of therapy, however, patient's blood glucose was consistently greater than 400 mg/dL. Unfortunately, she did not seek further medical attention.

After several days of severe hyperglycemia (>400 mg/dL), she presented to the emergency department with nausea, vomiting, and dizziness. She also reported a 2-day history of urinary frequency and polydipsia. On physical examination, the patient had sinus tachycardia and dry mucous membranes.

Cardiovascular, respiratory, gastrointestinal, and skin examination was unremarkable. Patient's point-of-care glucose check was >500 mg/dL. On laboratory workup, patient demonstrated a high anion gap metabolic acidosis with an anion gap of 24 mmol/L, bicarbonate 14 mEq/L, and pH 7.28. She also presented with a creatinine level of 1.7 mg/dL and a blood urea nitrogen of 60 mg/dL thought to be secondary to an acute kidney injury (AKI) secondary to intravascular volume depletion.

The patient was admitted to the ICU and initiated on intravenous insulin at a rate of 0.1 units/kg/h and fluids per our facilities' DKA protocol. In addition, a basic metabolic panel was ordered every 4 hours in conjunction with point-of-care glucose monitoring every hour. Patient's anion gap closed and she was transitioned to 15 units of Levemir insulin and stepped down to the medicine floor on day 2 of her hospital stay. Her blood glucose stabilized around 160 to 190 mg/dL and her AKI resolved after hydration on day 3. She was subsequently discharged on 2000 mg a day of metformin XR with 5 mg glipizide, a referral to Endocrinology, and instructions to stop alpelisib.

Discussion

Severe hyperglycemia can be a serious consequence of a PI3K inhibitor. Alpelisib acts by inhibiting the alpha subunit of the PI3K/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling pathway, which plays a critical role in cell growth, proliferation, metabolism, apoptosis, and cell survival.^{9,10} This pathway is also activated by the insulin receptor, which ultimately leads to the translocation of glucose transporter type 4 (GLUT4) to the cell surface resulting in intracellular glucose uptake and normoglycemia.¹¹ Blocking PI3K activity with alpelisib leads to temporary insulin resistance and hyperglycemia.¹² Those who already suffer from insulin resistance are susceptible to hyperglycemia crisis, such as DKA, if utilizing alpelisib.

Diabetic ketoacidosis is a rare but life-threatening consequence of hyperglycemia and can lead to coma or death.¹³ Mortality associated with this condition has been reported to be between 0.4% and 1.1%.¹⁴ We propose 5 steps to ensure that patients with prediabetes or well-controlled T2DM treated with alpelisib do not develop severe hyperglycemia and/or DKA. This is outlined below using the acronym S.U.G.A.R.

S—Strict Criteria: Do Not Use Alpelisib in Patients With Fasting Blood Glucose >140 mg/dL or A1c >6.4%

In the SOLAR-1 trial, those with type 1 diabetes and poorly controlled type 2 diabetes were excluded from the trial. Uncontrolled type 2 diabetes was defined as having a fasting plasma glucose level >140 mg/dL (7.7 mmol per liter) and a glycosylated hemoglobin level of >6.4 in the SOLAR-1

trial.³ Despite these strict inclusion criteria, 63.7% of patients reported hyperglycemia.³ This is especially alarming in a population that had adequate glucose control prior to the initiation of this drug. This highlights the need for providers to be prudent in who they choose to be a candidate for alpelisib.

Our patient's A1c was 8.0% prior to the initiation of alpelisib. We chose to initiate this drug based on the previous inclusion criteria of the SOLAR-1 trial, which was an HbA1c $\leq 8\%$.³ We were optimistic that her diligence to lifestyle modifications would prevent hyperglycemia; however, the powerful mechanism of insulin resistance in this drug was underestimated. Her tenuous clinical course gives support for a more stringent A1c criteria for alpelisib initiation.

U—Understand: Ensure That Patient Understands the Steps Needed to Prevent Hyperglycemia

Patients must understand the role that they play in preventing hyperglycemia. We recommend a written document be handed to the patient when starting alpelisib. This resource should include information on glucose monitoring (such as how to use a glucometer, where to pick up their glucometer and supplies, and how often to test fasting blood glucose levels), who to contact if blood glucose levels rise above 140 mg/dL, and common symptoms associated with hyperglycemia.

Our patient understood how to test her blood glucose levels, but on debriefing after discharge from the ICU, she was unsure about who to contact once her blood glucose levels increased. This was an essential breakdown in her care; without proper understanding of who to notify of hyperglycemia, the patient's care was delayed which resulted in the development of life-threatening DKA. This may be avoided in the future by ensuring the patients have proper understanding of glucose monitoring, contact resources, and hyperglycemia symptoms.

G—Get Help: Primary Care Provider and Endocrinology Assistance Is Essential

First, one must ensure their patient has a primary care provider (PCP). This will likely be the case, as the patient population we are discussing has prediabetes or T2DM and are possibly managed or monitored by a PCP but it is imperative to confirm. We recommend notifying the PCP that the patient will be starting alpelisib and informing them of the risk of hyperglycemia. This way, if patient develops hyperglycemia and help is required to start pharmacological intervention, PCP will be able to quickly aid in resuming euglycemia.

In addition, we recommend consulting endocrinology for grade 2 hyperglycemia (160-250 mg/dL) or higher. A facility protocol should be in place to allow for a prompt visit with this specialist, if needed. Many centers are overwhelmed and a referral placed to an endocrinologist may take weeks to be scheduled. We recommend the oncologist work in together

with the PCP and endocrinologist to bring awareness of how quickly hyperglycemia induced by alpelisib can occur and the need for rapid assessment and intervention.

Ideally, our patient would have informed her provider when she first noticed an upward trend of her glucose values. This would have enabled pharmacology intervention to be initiated, thus preventing severe hyperglycemia and DKA. At that time, an urgent follow-up with endocrinology may have also been considered.

A—Act Immediately: Initiate Treatment in Those With Hyperglycemia Early

In accordance with the SOLAR-1 protocol for the treatment of hyperglycemia, patients with grade 1 hyperglycemia (>140 - 160 mg/dL) should start or intensify metformin dosing. Patients should be started on 500 mg of metformin at dinner. If this is well tolerated, then the regimen can be intensified to 500 mg twice daily at dinner and breakfast.³

If patient develops grade 2 hyperglycemia (160-250 mg/dL), twice-daily metformin should be initiated for a total of 1500 mg daily (500 mg at breakfast and 1000 mg at dinner). If grade 2 hyperglycemia persists, we recommend consulting an endocrinologist for the addition of antiglycemic drugs (such as pioglitazone 30 mg).³

Grade 3 hyperglycemia calls for interruption of alpelisib and a prompt referral to endocrinology. Insulin may be used for several days until euglycemia resumes and then the initiation of metformin should be started, as outlined for grade 2 hyperglycemia.³ Alpelisib may be resumed concomitantly with antidiabetic medication if blood glucose levels return to <160 mg/dL. According to SOLAR-1 trial, if fasting blood glucose levels do not resume grade 1 or lower after 21 days of antidiabetic therapy and the confounding factors have been excluded, alpelisib should be permanently discontinued.³

Grade 4 hyperglycemia secondary to alpelisib should result in the permanent discontinuation of the drug, after all confounding factors have been ruled out.³ Measures should be taken to correct hyperglycemia and any electrolyte disturbances through immediate actions (such as fluids, insulin, and electrolyte replacement). If DKA is a concern, patient should be advised to go to the emergency room immediately.

Unfortunately, our patient's blood glucose levels were slowly rising during her second week of alpelisib use. Our patient waited 4 days to get emergency treatment with blood glucose values more than 400 with associated symptoms of critical hyperglycemia. Instead, she should have been counseled to "act immediately" and proceed to the nearest emergency room.

R—Record: Initiate Blood Glucose Logs in Those With Prediabetes or T2DM

It is important to catch hyperglycemia early; therefore, we recommend to check fasting blood glucose levels upon

waking twice weekly at minimum for 8 weeks and then weekly thereafter. This surveillance regimen differs slightly from the assessments conducted in the SOLAR-1 trial, as laboratory tests were completed at screening, on day 8 of enrollment, every 2 weeks from initiation for 8 weeks, and then monthly.³ In the highlighted case, our patient developed severe hyperglycemia very quickly and laboratory testing every 2 weeks would have been insufficient to prevent DKA.

These twice-weekly blood glucose values should be recorded in a log for review by the provider. The patient should be informed to contact their oncologist or PCP if values increase to more than 140 mg/dL so that metformin can be initiated and the patient be counseled on lifestyle interventions.

Our patient was able to record her fasting blood glucose values; however, without contacting the appropriate provider, an essential step in hyperglycemia prevention was compromised. This example speaks to the importance of ensuring all components of S.U.G.A.R are executed to prevent hyperglycemia in those most vulnerable.

Conclusion

We report a case of a woman with diet-controlled T2DM who developed DKA shortly after the initiation of alpelisib. This case highlights the multitude of steps required to prevent life-threatening hyperglycemia in those with preexisting prediabetes or T2DM prior to starting alpelisib. In summary, we recommend that the provider follows strict criteria when determining who can be started on alpelisib, ensures the patient understands prevention of hyperglycemia, works alongside PCP and endocrinologists when needed, acts quickly to initiate pharmaceutical interventions for adequate glycemic control, and has the patient record their blood glucose values for adequate interpretation. By implementing these steps, we hope to prevent critical hyperglycemic episodes in vulnerable patients on alpelisib.

Authors' Note

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

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