

Ketoacidosis in a Patient with Type 2 Diabetes Requiring Alpelisib: Learnings and Observations Regarding Alpelisib Initiation and Rechallenge

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Background: Diabetic ketoacidosis (DKA) is a rare complication of alpelisib, but cases of DKA are reported. Alpelisib's safety in patients with long-standing, suboptimally controlled diabetes is unclear since clinical trials of alpelisib did not include them.

Case: A case is presented on a patient with metastatic breast cancer and type 2 diabetes admitted for DKA eleven days after starting alpelisib. Since DKA is implicated in antihyperglycemics that inhibit sodium-glucose cotransporter-2 (SGLT2) inhibitors, her empagliflozin was discontinued. Alpelisib was also held since it was recently initiated. After the DKA resolved, she was discharged and restarted alpelisib. Within 4 hours of taking the first dose, the patient developed a second episode of DKA, and alpelisib treatment was stopped permanently.

Conclusion: Patients with long-standing type 2 diabetes are at high risk of alpelisib-induced Grade 3 and 4 hyperglycemia, including DKA. It is essential to communicate with non-oncology stakeholders about the risk of DKA with alpelisib as it can be overlooked for more common causes. Restarting alpelisib can result in severe hyperglycemia or DKA within 24 hours of the first dose. In this population, the risks associated with rechallenging alpelisib must be heavily weighed against its benefits. Before restarting alpelisib, a thorough evaluation of the appropriateness of the patient's antihyperglycemics and diet must occur to anticipate and mitigate a second event. Antihyperglycemics independent of the PI3K/AKT/mTOR pathway may be preferred agents. A plan should be in place to quickly respond to rising glycemia and early referral to a diabetologist or endocrinologist is recommended. Continuous glucose monitoring and hospital admission are recommended during rechallenge. A better understanding of alpelisib-induced hyperglycemia, especially in patients with diabetes, is required to navigate alpelisib treatment safely. Emphasis should be placed on patient education of symptoms and monitoring parameters.

Keywords: alpelisib, diabetes, SGLT2 inhibitors, ketoacidosis, breast cancer, hyperglycemia

Introduction

In patients with breast carcinoma, approximately 40% will have phosphatidylinositol-3 kinase (PI3K) dysregulation because of a mutation in the PIK3CA gene.¹ The phosphatidylinositol-3 kinases are a family of proteins responsible for cell proliferation, growth, survival, motility, and metabolism in the PI3K/AKT/mTOR signaling pathway. Activating mutations of the PI3K family are frequently found in cancers.² Alpelisib, an alpha-subunit PI3K inhibitor (PI3K α), provides a novel treatment that improves progression-free survival in patients with metastatic, hormone-receptor positive (HR+), HER 2-negative (HER2-), PI3K-mutated breast cancer that has progressed on endocrine-based therapy.³⁻⁵ Alpelisib is being studied in different subtypes and stages of breast cancer, other cancers, and non-malignant disorders. The results of these studies are awaited with interest.⁶⁻⁹

Alpelisib, coadministered with endocrine therapy, has generally been well tolerated. Hyperglycemia is well elucidated with inhibitors of the PI3K/AKT/mTOR pathway. In the Phase III clinical trial for alpelisib, SOLAR-1, grade 3 and 4 hyperglycemic events were recorded, including two cases of ketoacidosis.^{5,10}

Since alpelisib became available, there have been several published cases of DKA in alpelisib-treated patients regardless of the presence of diabetes at baseline.^{11–17} Only one case report involves a patient with diabetes and her alpelisib was discontinued shortly after the first DKA event.

Here, we present a case of DKA in a patient with long-standing type 2 diabetes. She is on multiple antihyperglycemics, including the sodium-glucose cotransporter-2 (SGLT2) inhibitor, empagliflozin. Eleven days after starting alpelisib 300 mg/day, she presented to the Emergency Department (ED) with DKA. Because the DKA was attributed to the SGLT2 inhibitor instead of alpelisib, it was discontinued during her admission. We hypothesize that the absence of SGLT2 inhibition contributed to a near-immediate second DKA event upon alpelisib rechallenge.

Case

A 58-year-old woman with metastatic HR+, HER2- breast cancer presented to the ED with a 3-day history of nausea and vomiting, dyspnea, rash, and blood glucose of 319 mg/dL. Her medical history included type 2 diabetes for which she took empagliflozin, metformin/sitagliptin, and gliclazide. A few weeks prior, molecular profiling revealed the presence of a PIK3CA gene mutation, and she started fulvestrant and alpelisib. Her metastatic breast cancer had already progressed on endocrine and chemotherapy treatment. At that time, self-recorded fasting blood glucose readings were 180–216 mg/dL, and HbA1c was 7.7% (61 mmol/mol). The patient was instructed to monitor blood glucose levels frequently. If glucose levels persistently increased, we would refer her to endocrinology for further management. A follow-up assessment occurred one week after alpelisib initiation, in which the patient reported weight loss of 2–3 kg, decreased appetite, and blood glucose readings ranging from 190 to 306 mg/dL. Before she could return for another follow-up, she began to vomit and presented to the ED three days later.

On presentation to the ED, the patient demonstrated dyspnea, nausea and vomiting, and a generalized maculopapular rash on her torso. Labs reported anion gap: 36 mEq/L, pH: 6.99, total CO₂: 6 mEq/L, glucose: 402 mg/dL, ketonemia and ketonuria. The patient was admitted to the hospital and started on an insulin sliding scale. Empagliflozin was thought to be a possible cause of the DKA by the ED team and was discontinued. Because alpelisib was recently started and implicated for the rash, it was also held during admission. The patient's condition worsened overnight, and she was transferred to the ICU. She received bicarbonate infusion and intravenous insulin as per the institutional DKA protocol. Upon resolution of the DKA, she was discharged six days after presentation to the ER. At that time, her gliclazide dose was increased to compensate for the discontinuation of empagliflozin.

Two weeks later, the patient returned to the oncology clinic to restart alpelisib. At the time of restarting alpelisib, her blood glucose levels had returned to baseline (180–216 mg/dL). To circumvent the rash development, she was instructed to take desloratadine 10 mg once daily starting two days before the first dose of alpelisib. Four hours after her first alpelisib dose, she returned to the ED. She described feeling unwell one hour after taking alpelisib and experienced emesis, dysphagia, and a pruritic rash on her abdomen, back, and thighs. Her self-monitored blood glucose readings indicated a rapid rise from 198 mg/dL to 306 mg/dL shortly after alpelisib administration. The patient was also febrile. Labs in the ED revealed anion gap: 20 mEq/L, CO₂: 21 mEq/L, glucose: 397 mg/dL with ketonemia and ketonuria. She was diagnosed with diabetic ketoacidosis, rash secondary to alpelisib, and possible pneumonia. She was started on DKA insulin protocol and antibiotics empirically. The next morning, the patient was transitioned to subcutaneous insulin and maintained on her diabetic medications as per admission. She defervesced quickly, and blood and urine cultures remained negative for infection. Her rash improved within days of alpelisib discontinuation. Endocrinology was consulted, and they started basal insulin with supplemental mealtime insulin. Alpelisib and gliclazide were discontinued. She was discharged six days after admission. Following her discharge, she did not have any further hyperglycemic complications.

Discussion

This case study highlights the rapidity of alpelisib-induced hyperglycemia and ketoacidosis in a patient with long-standing type 2 diabetes. Our patient, who was readmitted for ketoacidosis shortly after discharge from her first episode, exemplifies the challenge of identifying causality when two agents known to cause DKA are present. In addition, alpelisib is relatively new in Canada, while DKA induced by SGLT2 inhibitors is well recognized. Thus, the toxicity

profile of alpelisib may not be top of mind during the initial management of DKA. This case also highlights the caution required when alpelisib is prescribed for patients who do not meet the stringent criteria of pivotal trials.

Alpelisib, by inhibiting a kinase mediator of the PI3K/AKT/mTOR pathway, successfully inhibits cancer cell proliferation. In the Phase 3 trial, SOLAR-1 evaluated the combination of alpelisib and an endocrine agent, fulvestrant, versus fulvestrant alone. The study concluded alpelisib prolonged progression-free survival for women with HR-positive, PI3K-positive metastatic breast cancer. Alpelisib becomes a valuable option to further delay the need for chemotherapy, a treatment the patient did not desire. PI3K has also been recognized to have a role in glucose homeostasis and influences insulin's effect on muscle, liver, and fat.¹⁸ Under physiologic conditions, insulin activation of the PI3K pathway mediates glucose and lipid metabolism activities, such as translocation of the glucose transporter type 4 receptor to the cell surface, glucose uptake, glycogen synthesis, suppression of glucose output, triglyceride synthesis, and insulin-induced mitogenesis.¹⁹ When PI3K is inhibited, insulin is released in response to elevated blood glucose, but its downstream effects are diminished. As a result, glycogen synthesis and glucose uptake are reduced, leading to hyperglycemia.

In the SOLAR-1 trial, the all-grade incidence of alpelisib-induced hyperglycemia was 67%. Severe hyperglycemia and treatment discontinuation due to hyperglycemia were more common in patients with baseline hyperglycemia.³ In patients with no diabetes at baseline, 18.6% developed grade 3 or 4 hyperglycemia. In patients with elevated baseline fasting plasma glucose and HbA1c, 48.4% developed grade 3 or 4 hyperglycemia. About 60% of patients in the alpelisib arm of SOLAR-1 were considered prediabetic or diabetic. However, A1C had to be less than 6.4% and fasting blood glucose less than 138 mg/dL. Thus, recruited patients had stable and controlled Type 2 diabetes.^{3,20} Given that the trial excluded heavily treated or poorly controlled diabetes, it is suspected that the real-world incidence of DKA with alpelisib could be substantially higher.

Multiple case reports have been published regarding alpelisib-induced DKA, regardless of the presence of diabetes at the time of initiation (Table 1). Only one case, reported by Abufaied et al, discussed DKA in a patient with diabetes who was started on alpelisib. Their patient was a 64-year-old woman with type 2 diabetes controlled on metformin. Her HbA1c at baseline was 5.6% (38 mmol/mol). DKA occurred within two weeks of initiation of alpelisib. After recovery from her DKA, she was stabilized on multiple daily injections of insulin and metformin. While still in hospital, her alpelisib was reintroduced at 200 mg/day. Shortly after her first dose, her blood glucose peaked at 364 mg/dL, and her alpelisib was promptly discontinued.¹⁶ Similarly, in patients with prediabetes, alpelisib-induced DKA occurred within 7 to 14 days of initiating alpelisib.^{12,15,17} In this group of patients, reinitiating alpelisib occurred successfully, but significant hyperglycemia was observed within 24 hours of the first dose.¹²

Table 1 Case Reports of Severe Hyperglycemic Events Due to Alpelisib

Reference	Age	Presence of Diabetes at Baseline	Most Severe Adverse Event	Onset (Days)	Rechallenge	Rechallenge Outcome	Anti-Hyperglycemics Prescribed
Farah ¹¹	49	None	DKA	60	Yes	Hyperglycemia within 4 hours	Insulin, metformin
Carillo ¹²	66	Prediabetes	DKA	14	Yes, at lower dose (250 mg/d)	Hyperglycemia within 24 hrs	Insulin, metformin, empagliflozin
Fugere ¹³	48	None	DKA	26	No	N/A	N/A
Nguyen ¹⁴	73	None	DKA	11	No	N/A	N/A
Ahmed ¹⁵	66	Prediabetes	DKA	13	Yes, at lower dose (250 mg/d)	Hyperglycemia at 3 weeks	Insulin, metformin
Abufaied ¹⁶	64	Diabetes	DKA	14	Yes, at lower dose (200 mg/d)	Hyperglycemia (onset unknown)	Insulin, metformin
Jeun ¹⁷	55	Prediabetes	DKA	7	No	N/A	N/A

Abbreviations: DKA, diabetic ketoacidosis; N/A, not applicable.

Not all PI3K/AKT pathway drug inhibitors affect glycemic control equally. The PI3K α isoform target of alpelisib is notably influential in glucose and insulin homeostasis compared to other kinase inhibitors of the same pathway. Everolimus, an mTOR inhibitor, works downstream from PI3K and does not cause hyperglycemia to the same extent.¹⁰ Of note, our patient was treated with nine months of everolimus prior to alpelisib. During that period, she did not develop significant hyperglycemia. Thus, tolerance to other PI3K/AKT pathway inhibitors does not allow one to predict the magnitude of glucose deregulation induced by alpelisib.

Our patient was also on a SGLT2 inhibitor, empagliflozin, during her first admission for DKA. SGLT2 inhibitors prevent glucose reabsorption from the proximal renal tubules causing an increase in urinary glucose excretion. SGLT2 inhibitors have become attractive for type 2 diabetes given their cardioprotective effects with recognized reductions in cardiovascular deaths and hospitalization rates in patients with heart failure.^{21,22} However, the entire class of SGLT2 inhibitors was recently associated with a black box warning for increasing the risk of DKA. A US Food and Drug Administration advisory reported 73 cases of ketoacidosis with SGLT2 inhibitors in both those with and without diabetes.²³ Of interest, SGLT2 inhibitors are commonly associated with euglycemic DKA, where there are normal to near-normal glucose elevations (blood glucose <288 mg/dL at the time of the DKA).²⁴ DKA induced by SGLT2 inhibitors is uncommon, occurring at rates reportedly ranging from 0.16 to 0.76 events per 1000 patient years. The onset of SGLT2-induced DKA is inconsistent and can be triggered in patients who recently started and those long-stabilized on SGLT2 inhibitor treatment. The mechanism for SGLT2-induced DKA has been explained elsewhere.²⁵

At the time of diagnosis of our patient's first DKA episode, it was not feasible to distinguish the causative agent (empagliflozin versus alpelisib). However, the near-immediate development of the second DKA confirms that the first DKA episode was due to alpelisib and not empagliflozin. The onset of DKA upon alpelisib rechallenge suggests that the loss of SGLT2 inhibition may have been detrimental. A SGLT2 inhibitor's antihyperglycemic effect should be suitable for alpelisib. Its action reduces glucose via a mechanism outside the PI3K/AKT/mTOR pathway. Its own association with DKA exposes the need for more experience and information on the safety of SGLT2 inhibitors when used with PI3K inhibitors. Several case reports on the success of SGLT2 inhibitors have been published in patients with alpelisib-induced hyperglycemia.^{26–29} In contrast, a report of euglycemic DKA in a patient starting canagliflozin while taking the PI3K α inhibitor, taselisib, reinforces the need to remain vigilant.²⁹ Insulin and its secretagogues, sulfonylureas, and meglitinides all rely on the PI3K/AKT/mTOR pathway for their antihyperglycemic effect. It has been postulated that such agents have lower efficacy against PI3K-inhibitor-induced hyperglycemia, although they are still recommended for use.^{12,20,30} Due to its mechanism of action, there is some concern that insulin and secretagogues may attenuate the anticancer effect of PI3K inhibitors.^{30,31} While this effect has not been addressed in large clinical trials and is hypothetical to date, it is further incentive to look at agents other than insulin and secretagogues to manage hyperglycemia from PI3K inhibitors.

It is also important to point out the differences in onset between our patient's first and second episodes of DKA. In the SOLAR-I trial, the median time of hyperglycemia onset after initiation of alpelisib was 15 days with a range of 5–395 days.²⁰ Consistent with this observation, our patient presented to the hospital 11 days after drug initiation. However, on restarting therapy after the DKA resolved, profound hyperglycemia and a second DKA event occurred within 4 hours of the first dose. Drawing similarities between our case and other case reports, hyperglycemia develops quickly when alpelisib is restarted after a treatment interruption. The explanation for this is unknown but appears reversible. Patients return to baseline glycemic control 3–5 days after stopping alpelisib.^{13,14,16} Persistent hyperglycemia and hyperinsulinemia quickly exacerbate tissue and hepatic insulin resistance, a complex physiological phenomenon involving the PI3K/AKT/mTOR pathway.^{32,33} A possible theory is that alpelisib worsens hepatic and peripheral insulin resistance, leading to a greater dependency on the PI3K/AKT/mTOR pathway. Animal studies have shown that aggravated insulin resistance can occur within 48 hours of exposure to persistent hyperglycemia and hyperinsulinemia.³⁴ After the resolution of the first DKA, and with an intact PI3K/AKT/mTOR signalling pathway, the heightened state of insulin resistance is covert and manageable with antihyperglycemics. Reintroduction of alpelisib, however, stops PI3K/AKT/mTOR signaling and immediately exposes the heightened insulin-resistant state. In our patient, previously reliant on an SGLT2 inhibitor for glucose control, the loss of an antihyperglycemic that functions outside of the PI3K/AKT/mTOR pathway may contribute to the speed at which she developed her 2nd DKA. Further study is necessary so that clinicians can learn how to mitigate the severe and rapid response to alpelisib re-exposure.

Of the reported patients with alpelisib-induced DKA who were rechallenged, only our patient developed a second episode of DKA. Our case highlights several learning points for our team. Firstly, severe hyperglycemia and DKA during an alpelisib rechallenge should be anticipated. The incidence is higher in patients with diabetes. Rechallenging in the hospital or a similarly monitored environment should be strongly considered. Secondly, the restoration of euglycemia prior to rechallenge is insufficient to control or slow the development of a second grade 3 or 4 hyperglycemic event. Our patient's dose of gliclazide, a sulfonylurea, was increased after the SGLT2 inhibitor empagliflozin was discontinued. While this increased dosage improved blood glucose control in the two weeks before restarting alpelisib, it was insufficient once alpelisib was reinitiated. Thirdly, patients should be provided with some form of communication directed to ED clinicians regarding the potential for DKA with alpelisib so that it is not overlooked. Communication is even more essential if the patient is on another drug associated with ketoacidosis (eg, SGLT2 inhibitors, atypical antipsychotics, and illicit drug use). Given the number of reports of alpelisib-induced hyperglycemia and DKA, proper education and monitoring cannot be highlighted enough. Patients, with or without diabetes, should be educated on symptoms of severe hyperglycemia and ketoacidosis. Early involvement of the diabetologist or endocrinologist in patients with diabetes or prediabetes is advised.

There are several possible theories about why our patient's alpelisib reintroduction caused DKA. Our patient was re-established on full-dose alpelisib instead of a lowered dose and had a long history of type 2 diabetes compared to the other reported cases, and her diabetes control was dependent on antihyperglycemic agents that worked outside of the PI3K/AKT pathway. We believe that our patient benefited from the SGLT2 inhibitor and that its omission may have contributed to a near-immediate second DKA. Whether a low-carbohydrate diet could have further slowed the rate of glucose rising is worthy of consideration, especially since it led to a successful reintroduction of alpelisib in a previous patient without diabetes.¹² Patients who are heavily treated with antihyperglycemic agents or have sub-optimally managed diabetes may not be good candidates for alpelisib. A better understanding of minimizing and managing alpelisib's hyperglycemic effects is needed. However, to preserve PI3K α inhibitors as a line of therapy for this patient population, further research into their mechanisms of toxicity is vital. Continued sharing of successful rechallenge practices of alpelisib and other PI3K α is encouraged.

Conclusion

Our case presentation highlights the need for caution when initiating alpelisib in patients with diabetes or prediabetes. A proactive plan for monitoring and managing hyperglycemia should be in place and shared among all vital stakeholders before implementing alpelisib. Educating patients and non-oncology stakeholders regarding the risk of DKA with alpelisib should be implemented. A thorough evaluation of the appropriateness of the patient's antihyperglycemics and diet must occur before restarting alpelisib to anticipate and mitigate toxicity. Hospital admission is advised for patients who developed severe hyperglycemia or DKA and is preparing to restart alpelisib.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Ethics and Consent Statements

Local institutional REB approval requirements were reviewed and waived because this publication involves a single case report for publication and does not qualify as human subject research. Consent has been obtained from the patient to publish this case.

Author Contributions

All authors made a significant contribution to the work reported, whether that is the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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