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Alpelisib-Induced Hyperglycemic Emergencies

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Abstract

Background: Hyperglycemia is the most common adverse effect of the anti-cancer drug alpelisib, an inhibitor of phosphatidylinositol-3-kinase (PI3K).

Main objective: To describe a woman presenting with alpelisib-induced hyperglycemic emergency and other similar cases reported in the literature.

Secondary objective: To discuss the status of sodium-glucose cotransporter-2 (SGLT-2) inhibitors, ketogenic diet and insulin for alpelisib-induced hyperglycemia.

Methods: Pubmed research up to May 3, 2023. Search terms included alpelisib, hyperglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic state, SGLT-2 inhibitors, ketogenic diet, insulin. Clinical trials, case reports, pertinent review articles and animal studies, and pre-print articles were reviewed.

Results: 17 cases of hyperglycemic emergencies, including ours, were described. Nine cases were presented with diabetic ketoacidosis (DKA) and 2 cases with mixed DKA and hyperosmolar hyperglycemic state (HHS). Six of the 17 patients (35%) had no history of diabetes. The median time from initiation of alpelisib to diagnosis of hyperglycemic emergency was 2 weeks (range 7-69 days). All patients were treated successfully with intravenous (IV) fluids and insulin. In 2 patients, DKA recurred 4 h and 5 days after re-starting alpelisib. Anecdotal data suggest that use of SGLT-2 inhibitors and ketogenic diet might be effective in controlling alpelisib-induced hyperglycemia. Yet, these 2 treatment strategies may predispose DKA. Animal studies suggest that exogenous insulin might decrease the anti-tumor efficacy of alpelisib.

Conclusions: Alpelisib-induced hyperglycemia can proceed to hyperglycemic crises even in patients without a history of diabetes. Physicians and patients should be aware of this complication to avoid any delay in its diagnosis. Until more data becomes available, SGLT-2 inhibitors and ketogenic diet should be used with extreme caution in alpelisib-induced hyperglycemia.

Keywords: Alpelisib; Hyperglycemia; Hyperglycemic emergency; Diabetic ketoacidosis; SGLT-2 inhibitors; Ketogenic diet

Abbreviations: PI3K: Phosphatidylinositol-3-Kinase; SGLT-2: Sodium-Glucose Cotransporter-2; DKA: Diabetic Ketoacidosis; HHS: Hyperglycemic State; IV: Intravenous; HR: Hormone Receptor: HER2: Human Epidermal Growth Factor Receptor 2; FDA: Federal Drug Administration; FPG: Fasting Plasma Glucose

Introduction

Approximately 40% of women with hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer have activating mutations in the gene called PIK3CA [1]. In such patients, the anti-cancer drug, alpelisib inhibits tumor growth by blocking the PIK3 pathway [1]. In the meantime, insulin exerts its anti-hyperglycemic actions through the PI3K signal transduction pathway [2]. It follows that alpelisib intake may cause severe insulin resistance and subsequent hyperglycemia [1,2]. Hyperglycemia therefore is considered an expected "on-target" adverse effect of alpelisib [1]. In May 2019, the Federal Drug Administration (FDA) approved Alpelisib (Piqray) in combination with fulvestrant (estrogen receptor antagonist) for treatment of postmenopausal women, and men, with HR-positive, and HER2-negative, PIK3CA-mutated, advanced or metastatic breast cancer [3]. This approval was based on the positive results obtained with alpelisib in a landmark phase 3 randomized trial, the SOLAR-1 trial [1]. The most frequent adverse effect reported in SOLAR-1 trial was hyperglycemia. Thus, grade 3 hyperglycemia defined as fasting plasma glucose (FPG) of 161-250mg/dl, and

grade 4 hyperglycemia defined as FPG >500 mg/dl were recorded in 3.6.% and 0.6% in the alpelisib and placebo group, respectively [1]. Furthermore, the most frequent adverse effect leading to the discontinuation of alpelisib was also hyperglycemia (6.3% versus 0.0% in the placebo group) [1]. This is unfortunate because alpelisib exposure intensity had an impact on its anti-cancer efficacy. In fact, in SOLAR-1 trial, longer median progression free survival of breast cancer was observed in patients who received a higher median dose intensity of alpelisib (≥248mg/day) compared with lower median dose intensity (<248mg/day), 12.5 and 9.6 months, respectively [1]. In clinical practice, the incidence and severity of alpelisib-induced hyperglycemia is likely much higher than in SOLAR-1 trial because patients with type 1 diabetes and uncontrolled type 2 diabetes (FPG >140mg/dl, and HbA1c > 6.4%) were excluded from the trial [1]. Indeed, following the release of alpelisib in the market, several cases of hyperglycemic crises, DKA or HHS, were reported. The main purpose of this article is to describe once such case and summarize features of other reported cases in order to alert physicians about the early diagnosis and treatment of this life-threatening complication [4]. In addition, the author discusses some controversial strategies for treatment of alpelisib-induced hyperglycemia, namely SGLT-2 inhibitors, ketogenic diet and insulin.

Case Report

A 37-year-old female had 2 year-history of breast cancer metastatic to bones. She was diagnosed with type 2 diabetes one year ago and was treated with metformin (1000mg twice daily) and glimepiride 2mg every morning. Two weeks after starting alpelisib 300mg/d, and during her oncology follow-up clinic visit, she had no complaints. Yet, her laboratory results on that day showed severe hyperglycemia with plasma glucose (PG) of 403mg/dl, and biochemical evidence of DKA with elevated serum β-hydroxy butyrate 6.14mmol/L (normal ≤ 3.0mmol/L), serum bicarbonate of 13mmol/L (normal 22-32mmol/L), venous pH of 7.28 (normal 7.33-7.43) and an anion gap of 18mmol/L (normal 4-14mmol/L). Her glycated hemoglobin (HbA1c) levels on admission were 9.4%, which markedly worsened from her previous HbA1c of 7.7% documented approximately 45 days before starting alpelisib. The patient was admitted to intensive care unit, received IV insulin and IV fluids as per our hospital protocol. Alpelisib was discontinued. DKA resolved in approximately 24h. She was discharged on insulin glargine 30units qAM in addition to metformin 1000mg bid.

Description of Cases

Review of literature revealed 16 women of alpelisib-induced hyperglycemic crises [5-15] (Table 1). Five cases were reported in the pre-print article by Wintraub et al. [15]. After adding our case, 8 of 17 subjects (47%) had history of type 2 diabetes, 3 (6%) had pre-diabetes (HbA1c 5.7-6.4%), and 6 (35%) had no known history of diabetes, (Table 1). They had a wide age range from 37 to 73 years old. In the majority of subjects, the type of hyperglycemic crisis was DKA. However, 2 patients were presented with a mixture of DKA and HHS [5,10] (Table 1). The time between the beginning of alpelisib administration and the presentation of hyperglycemic emergency ranged from 1 week to 69 days, median 2 weeks (Table 1). Interestingly, in SOLAR-1 trial median time to onset of grade ≥3 hyperglycemia was very close, 15 days [16]. Alpesilib was discontinued as result of hyperglycemic emergency in 9 cases and was continued after decreasing its doses to 200 or 250mg/d in 2 cases (Table 1). Of note, recurrence of hyperglycemia was described in 2 patients [4,8] (Table 1). In fact, in the patient reported by Leung et al. [8], recurrence of DKA was observed only 4 hours after re-challenge with alpelisib. Most authors of these case reports measured anti-pancreatic β-cell antibodies and C-peptide levels to find out whether DKA could be the result of an autoimmune reaction or new-onset type 1 diabetes triggered by alpelisib. In all cases, β-cell antibodies were negative and C-peptide levels were normal or elevated, a pattern that is consistent with type 2 diabetes and not autoimmune or type 1 diabetes [17].

Table 1: Cases of alpelisib-induced hyperglycemic emergencies.

Reference, Patient's Age	Diabetes Status, Baseline HbA1c	HbA1c on DKA Presentation	Time from Starting Alpelisib to DKA	Acute Management Besides Insulin	Comments
1.Carrillo et al. [5], 66	Pre-diabetes, HbA1c 6.3%	9.40%	2 weeks	Alpelisib discontinued with normalization of BG within 14 days	Patient had mixture of DKA + HHS (plasma glucose 1,137 mg/dl, Serum osmolality 330 mOsm/kg)
2. Farah et al. [6], 49	No diabetes, HbA1c: NR	11.00%	2 months	Metformin. Reduction in alpelisib dose to 200 mg/d	
3. Nguyen et al. [7], 73	No diabetes, HbA1c NR	8.30%	8 days	Apelisib discontinued	
4. Leung et al. [8], 58	Type 2 diabetes, 7.7%	NR	11 days	Alpelisib held for 2 weeks. Had DKA recurrence 4 h after re-starting alpelisib.	Patient was taking empagliflozin, which was discontinued after DKA.

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5. Al Zeyoudi et al. [9], 45	No diabetes, 5.6%	6.40%	9 days	Normalization of BG 5 days after discontinuation of alpelisib	
6. Chafai et al. [10], 72	Pre-diabetes, 5.9-6.2%	10.60%	69 days	Permanent discontinuation of alpelisib	Patient had mixture of DKA + HHS (plasma glucose 960 mg/dl, Serum osmolality 327 mOsm/kg)
7. Fugere et al. [11], 48	No diabetes, 5.7%	8.80%	26 days	Permanent discontinuation of alpelisib	
8. Abufaied et al. [12], 64	Type 2 diabetes, 5.6%	NR	2 weeks	Permanent discontinuation of alpelisib after recurrence of hyperglycemia with 200 mg of alpelisib	Blood glucose rose to 280-320 mg/dl after restarting lower dose of alpelisib
9. Ahmed et al. [13], 66	Pre-diabetes, 6.4%	9.60%	13 days	Control of hyperglycemia by chronic treatment with insulin + metformin	Alpelisib dose was reduced to 250 mg/d 3 weeks after resolution of DKA
10. Jeun et al. [14], 55	No diabetes, 5.6%	NR	1 week	Permanent discontinuation of alpelisib	Patient was discharged on metformin
11. Thomas et al. [15], 76	Type 2 diabetes, 8.0%	NR	Approximately 20 days	Permanent discontinuation of alpelisib	Patient was discharged on metformin + glipizide
12. Weintraub et al. [15], age NR	Type 2 diabetes	NR	10 days	Alpelisib resumed after resolution of DKA.	DKA was asymptomatic. Patient was on SGLT-2 inhibitor which was discontinued
13. Weintraub et al. [15], age NR	Type 2 diabetes	NR	NR	Permanent discontinuation of alpelisib	
14. Weintraub et al. [15], age NR	Type 2 diabetes	NR	43 days	Alpelisib resumed after DKA	Patient was on SGLT-2 inhibitor which was discontinued. Recurrence of DKA 5 days after resumption of alpelisib
15. Weintraub et al. [15], age NR	Unknownn history of diabetes	NR	8 days	Permanent discontinuation of alpelisib	
16. Weintraub et al. [15], age NR	Type 2 diabetes	NR	14 days	Permanent discontinuation of alpelisib	
17. Present case, 37	Type 2 diabetes, 7.7%	9.40%	2 weeks	Alpelisib was discontinued	DKA was asymptomatic. Patient was discharged on metformin + insulin

Risk Factors of Alpelisib-Induced Hyperglycemia

In the SOLAR-1 trial, grades 3 and 4 hyperglycemia were more common in older patients ≥ 75-year-old (55.9%) versus younger subjects (35.6%) [16]. Moreover, proportions of patients with hyperglycemia in the alpelisib group were more common in those who were overweight (73.8%), or obese (67.6%) at baseline compared with those with a normal body index (BMI) (57.3%) [16]. In a retrospective study of 92 patients with metastatic breast cancer, Ge et al. [18] found that risk of grade 2-4 hyperglycemia (FPG > 161mg/dl) with alpelisib use was independently increased with pre-existing diabetes odds ratio (OR) 3.75 (95% CI 1.40-10.01), pre-diabetes (OR 6.22, 95% CI, 1.12-34.47), Asian ancestry (OR 7.10, 95% CI 1.75-28.84), and each unit of BMI above 20 (OR 1.17, 95% CI, 1.07-1.28). In another retrospective study, Liu et al. [19] identified HbA1c levels > 5.7% and BMI ≥25kg/m^2 as risk factors for hyperglycemia with use of inhibitors of PI3K and protein kinase B (AKT). The latter drugs also interfere with insulin signal transduction pathway [19].

Management Strategies of Alpelisib-Induced Hyperglycemia

Close monitoring of blood glucose (BG) values is essential in all patients starting alpelisib irrespective of previous diabetes status. In the SOLAR-1, FPG was assessed at screening, on day 8, every 2 weeks for the first 8 weeks, and then every 4 weeks [1]. Alpelisib was continued without dose adjustment if FPG was < 250mg/dl [16]. Meanwhile, if FPG did not resolve to <160mg/dl by anti-hyperglycemic treatment, alpelisib dose reduction was done. Anti-hyperglycemic therapy in SOLAR-1 included metformin, pioglitazone, and insulin as rescue medication. In addition, alpelisib was discontinued if FPG rose above 250mg/dl and endocrinology consult was recommended [16]. In addition to these measures, the author recommends patient education

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about early symptoms of hyperglycemic emergencies (polyurea, polydipsia, dizziness and fatigue). Moreover, every patient should have a glucometer to check her BG at least once daily after starting alpelisib. Furthermore, in patients with risk factors for alpelisib-induced severe hyperglycemia mentioned in the previous paragraph (i.e those with pre-existing diabetes, obesity, elderly) should preferably have a continuous glucose monitoring (CGM) device if possible. Anecdotal data suggest that SGLT-2 inhibitors and ketogenic diet might be particularly effective while insulin could be counterproductive for treatment of alpelisib-induced hyperglycemia. These issues are discussed below.

SGLT-2 inhibitors

Some investigators recommend using SGLT-2 inhibitors for treatment of alpelisib-induced hyperglycemia [20,21]. This recommendation was based on their animal experiments showing that SGLT-2 inhibitors effectively minimized the hyperglycemia and hyperinsulinemia induced by PI3K inhibitors and "dramatically" enhanced the efficacy of PI3K inhibitors against multiple tumor models [20,21]. Additionally, Blow et al. [22] reported rapid amelioration of BG levels by SGLT-2 inhibitors in 2 patients with alpelisib-induced hyperglycemia. Moreover, the in vitro and animal studies by Zhou et al. [23] suggested that SGLT-2 inhibitors decrease cancer growth, including breast cell lines. However, it is premature to recommend SGLT-2 inhibitors for prevention or treatment of alpelisib-induced hyperglycemia due to several reasons. First, it is well-known that SGLT-2 inhibitors themselves may rarely cause DKA, which may be "euglycemic" in some cases, i.e BG < 250mg/dl [24]. Second, it has been shown that incidence of alpelisib-induced DKA may be increased with use of SGLT-2 inhibitor. Thus, Weintraub et al. [15] estimated the incidence of DKA to be 24 cases per 100-years when alpelisib was taken with SGLT-2 inhibitor, much higher than the incidence of DKA with alpelisib + non-SGLT2 inhibitors (7 DKA cases per 100 patients-year), and with alpelisib only (4 cases per 100 patient-years). Indeed, in the latter study, 2 of the 5 DKA cases induced by alpelisib were taking an SGLT-2 inhibitor [15]. In addition, the patient reported by Leung et al. [8] and another reported by Liu et al. [25] were taking the SGLT-2 inhibitor empagliflozin, and yet developed DKA after starting alpelisib. Furthermore, Bowman et al. [26] described a 69-year-old woman who developed DKA 5 days after starting the SGLT2 inhibitor canagliflozin in small dose (100 mg qday) for treatment of hyperglycemia induced by the PI3K inhibitor taselisib. Therefore, until more safety data are available, SGLT2 inhibitors should be used with extreme caution and under close monitoring of BG in patients taking alpelisib.

Ketogenic diet

Ketogenic diet, i.e. a low carbohydrate diet usually less than 50gm carbohydrate/d may virtually decrease the hyperglycemic response to alpelisib because it depletes liver glycogen stores and subsequent glycogenolysis and hyperglycemia [2]. In addition, available evidence suggests that ketogenic diet may have beneficial effects in many cancers including breast cancer [27]. Indeed, several clinical trials are underway to evaluate the ketogenic diet as an adjuvant therapy in patients with breast cancer [27]. In 2 patients with breast cancer receiving alpelisib, Blow et al. [22] found that use of very low carbohydrate diet in one patient, and a combination of SGLT2 inhibitor + carbohydrate restriction in another patient was effective in rapid control of BG levels. Moreover, in animal and in vitro studies, Hopkins et al. [20] demonstrated that administration of ketogenic diet for 10 days in mice enhanced the efficacy of multiple PI3K inhibitors. They hypothesized that the latter finding could be attributed to the reduction of hyperinsulinemia and hyperglycemia (called insulin feedback) induced by PI3K- inhibitors [20]. Meanwhile, it should be emphasized that ketogenic diet may predispose to development of DKA when used in combination with SGLT-2 inhibitors [28]. Therefore, further studies are needed to establish the safety of this combination in alpelisib-treated patients.

Insulin

In animal and in vitro investigations, the group of Hopkins et al. [20,21] found that addition of insulin "dramatically" reduced the therapeutic effect of PI3K inhibitors. They attributed this observation to the possibility that exogenous insulin might override the inhibitory effect of PI3K inhibitors on insulin signal transduction pathway. Clearly, if this finding is replicated in humans, insulin therapy would decrease the anti-cancer efficacy of alpelisib. Until human studies are available, the author recommends insulin therapy for alpelisib-induced severe degrees of hyperglycemia (e.g., when BG > 300mg/dl and/or HbA1c is > 10.0%). In hyperglycemic crises, insulin remains the mainstay of therapy in addition to IV fluids [4].

Conclusions

Hyperglycemia is the commonest adverse effect of alpelisib, and the most frequent cause of drug discontinuation. This hyperglycemia may proceed to hyperglycemic emergencies, mainly DKA. All reported cases with alpelisib-induced DKA or mixture of DKA and HHS recovered completely with standard therapy [4]. Unfortunately, 53% of these patients discontinued alpelisib as result of hyperglycemic crisis. Close monitoring of BG at home and patient education about early symptoms of DKA should decrease the incidence and avoid delay in treatment of this hyperglycemic emergency. Equally important, oncologists should be familiar with alpelisib-induced hyperglycemia and consult endocrinologists for its management. Limited data regarding the beneficial use of SGLT-2 inhibitors for treatment of alpelisib-induced hyperglycemia is based on experimental studies. On the contrary, in humans, SGLT-2 inhibitors might precipitate DKA, particularly when combined with a ketogenic diet.

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Current Needs

Several phase 2 trials are underway to test the effects of ketogenic diet, the SGLT-2 inhibitors (dapagliflozin and canagliflozin) and metformin on reducing alpelisib-induced hyperglycemia [29-32]. The Targeting Insulin Feedback to Enhance Alpesilib (TIFA) will compare head-to head canagliflozin with ketogenic diet [29]. Further investigations are needed to evaluate insulin therapy for alpelisib-induced hyperglycemia to see whether such therapy might interfere with anti-tumor efficacy of alpelisib.

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