ORIGINAL RESEARCH

Alpelisib associated Diabetic ketoacidosis – learning from Real world data

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Abstract
Introduction and aim: Alpelisib is approved for metastatic breast cancer with phosphatidylinositol-3 kinase subunit alpha mutation. While hyperglycaemia is a common complication of Alpelisibuse , Diabetic ketoacidosis is rare . With increasing number of patient being provided the benefit of this drug , the number of cases being reported with DKA are also increasing in number . With this study we aimed to identify and expand the spectrum of clinical picture for this condition
Methods: Data from consecutive emergency admission with a diagnosis of Diabetic ketoacidosis was analysed for patients with breast cancer and on Alpelisib . Those with associated secondary factors for Diabetic ketoacidosis were excluded . A total of 5 cases were considered forfinal analysis.
Results : We observed diabetic ketoacidosis in one non diabetic and four well controlled type 2 diabetic patients.Most patient developed diabetic ketoacidosis within 30 days of Alpelisibinitiation . Nausea and vomiting were the most common presentation. On discontinuation of the drug , hyperglycaemia resolved within 3 days . Ondrug rechallenge at a lower dose of 250 mg , all patient developed hyperglycaemia but only one patient redeveloped diabetic ketoacidosis , Rest of patient were well controlled on a combination of oral antidiabeitic drugs with only one patient requiring insulin
Conclusion: Alpelisib is a promising drug for eligible patients of metastatic breast cancer ,however these patients should be closely monitored for hyperglycaemia . Diabetic ketoacidosis is a rare complication and require multidisciplinary approach to manage . Most patients can be managed well with oral antidiabetic agents once diabetic ketoacidosis resolves.
Keywords - alpelisib, diabetic ketoacidosis, hyperglycemia, breast cancer, adverse drug events

Introduction and Background

Alpelisib is an inhibitor of the Alpha subunit of phosphatidylinositol-3 kinase (PI3K) which has been approved as a novel treatment in patients with metastatic, hormone-receptor positive (HR+), HER 2-negative (HER2-), breast cancer with mutations in phosphatidylinositol 3-kinase catalytic subunit alpha (PIK3CA) that has progressed on endocrine-based therapy.(1) Effective of this molecule was established in SOLAR -1 trial which showed an improvement in progressive free survival when patient were put on Alpelisib regardless of the dose.(2) With the increasing detection and incidence of breast cancer a newer molecule such as Alpelisib provides a much needed increase in the armamentarium against breast cancer , however it comes at the cost of side effects associated with it .

Due to its inherent mechanism of action leading to inhibition of PI3K , which is activated during insulin action , alpelisib is associated with hyperglycaemia as one of the most common side effects ranging from 59-62% in with grade3 or 4 hyperglycaemia being reported in 28% of patients . (3,4,5)Diabetic ketoacidosis (DKA) reported with alpelisib has been reported however it remains a rare occurrence but has been reported in both diabetic and non diabeticindividuals .(6,7,8).

While Alpelisib is associated with a better progression free interval amongst patient with breast cancer , one of major and frequent side effect is hyperglycaemia. Here we shall discuss a few cases where introduction of Alpesilib led to development of life threatening hyperglycaemia leading to diabetic ketoacidosis.

Here we present five cases of diabetic ketoacidosis presenting in patients of breast cancer that developed post initiation of Alpelisib in fourpatient with preexisting diabetes and one patient without any history of diabetes.

Methodology

Data for consecutive admissions for diabetic ketoacidosis from two tertiary care referral centres

was collected for analysis with follow up data being obtained on OPD visits during period of April 2022 to Dec 2023

Inclusion criteria

Patients on Alpelisib with h/o diabetic ketoacidosis presenting in Endocrinology department.

Exclusion criteria

1. Patients with diabetic ketoacidosis not on Alpelisib
2. Patients on Alpelisib presenting with diabetic ketoacidosis with secondary confounding factors as trigger for Diabetic ketoacidosis

Diabetic ketoacidosis was diagnosed on the following basis

1.Ketonaemia 3 mmol /l and over or significant ketonuria (more than 2 + on standard urine sticks)

2. Blood glucose over> 250 mg

3. Venous bicarbonate (HCO3)) below 15 mmol /l and /or venous pH less than 7.3 (

Overall8 patients were considered. However 3 patients were excluded from analysis due to associated urosepsis in one patient, pneumonia in second patient and lack of compliance to insulin in the third patient . A total 5 patient were included as part of thisobservational study. Demographic data as well as clinical data was collected as available from hospital records . Follow up data was captured on subsequent visits of the patient to the opd.

Ethics Statement

The study was conducted in accordance with the ethical principles laid down by the Declaration of Helsinki ICH-E6 R2 'Good Clinical Practice' guidelines. Written informed consent was obtained from all patients before enrolment. Protocol was approved by the institutional review board (IRB/15/2023 and IEC/23/065-OBG)

Results

The demographic, biochemical and clinical characteristics of all the cases are described in table 1.

Case 1

A 54 year old female with history of b/l mastectomy for breast cancer in 2016 . Following which she was put on anastrazole and radiation therapy and obtained remission .Howeverin july 2023 PET CT showed two metastasis lesion in her spine . She was confirmed to be a case of PI3KCA mutation and initiated on Alpesilib . There was no previous history of type 2 diabetes and her HbA1c one month prior was 5.6% . Her BMI was 26.4 kg/m^2 . Two weeks after initiation of Alpesilib , she presented to the opd with increased thirst , pain abdomen and one episode of vomiting . Her RBSon admission was 597 mg/dl . Her arterial blood gases study showed a pH of 7.16, pCO2 15 mm.Hg, HCO3 5.9 mmol/l, anion gap 25, urine ketones were 4 + consistent with diagnostic findings of DKA.

She was initiated on IV fluid and insulin drip and Alpelisib was discontinued . Patients glycaemic parameters improved and she was transitioned to subcutaneous insulin with resolution of ketosis by 48 hr of hospital stay . After discussing with oncology team ,Alpesilib was reinitiated in dose of 250 mg/day on day 6 of her hospitalisation . She was managed with a combination of insulin lispro, glargine , sitagliptin , metformin and pioglitazone with oral antidiabetic agents(OAD) being added on subsequent opd visits . After 3 months , her hba1c was 6.9 % patient was off lispro with glimeride being added to her treatment regimen

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Fig 1 - The demographic , biochemical and clinical characteristics of the cases

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (in yr)	54	58	48	81	61
Time since diagnosis (in yr)	8	6	8	17	11
Type of diabetes	Non diabetic	Type 2 diabetes	Type 2 diabetes	Type 2 diabetes	Type 2 diabetes
Initial Hba1c %	5.6	7.9	6.2	7.3	7.1
Duration of Alpelisib treatment before onset of DKA	14 days	10 days	17 days	62 days	21 days
RBS(mg/dl) on presentation	597	487	449	612	360
Arterial pH	7.06	7.15	7.11	7.01	7.26
HCO3-(mmol/l)	10.6	11.2	4.4	4.9	12.6
pCO2 mmhg	5.9	26	11	7.8	18
Urine ketones	++++	+++	+++	++++	+++
Initial DM medication	none	linagliptin, metformin and gliclazide	gliclazide , metformin and sitagliptin	Metformin ,vildagliptin,da pagliflozin	Metformin
Signs and symptoms of	Increased thirst	Nausea ,	nausea ,	Nausea,	Nausea ,

DKA	,tachypnea,pain abdomen and vomiting	vomiting , ketone breath	vomiting , dyspnea and rash	vomiting ,unconsciousness, hyponatremia	vomiting
Time to hyperglycaemia resolution	24 hr	36 hr	72 hr	45 hr	30 hr
Response to Alpelisib reintroduction	Hyperglycaemia but no DKA	Hyperglycaemia but no DKA	Recurrent DKA	Hyperglycaemia but no DKA	Hyperglycaemia but no DKA

Case 2

58 year old female presented to the emergency with h/o nausea and vomiting since 1 day prior. Patient was a known case of HR+/HER – breast cancer and type 2 diabetes. She had been recently started on Alpelisib and fulvestrant 10 days back after confirmation of PIK3CA mutation. Her Hba1c on that visit was 7.9 % and she was on linagliptin , metformin and gliclazide. Her RBS on admission in emergency was 487 . Her laboratory data was pH 7.15, pCO2 26mm.Hg, HCO311.2 mmol/l, anion gap 23 and urine ketones were 3+.

She was initiated on IV fluid and insulin drip and Alpelisib was discontinued . Patients glycaemic parameters improved and she was transitioned to subcutaneous insulin after 36 hr of hospital stay. Alpelisib was reinitiated at 250 mg by the oncologist 2 weeks after discharge. She was managed with insulin glargine (U300), linagliptin, metformin, gliclazide, voglibose and pioglitazone. After 3 months of follow up her hba1c was 7.1 %.

Case 3

48 yr female with metastatic breast cancer presented with complaints of nausea, vomiting, dyspnea and rash. She had been started on Alpelisib17 days back after testing positive for PIK3CA gene mutation. She was already a known c/o Type 2 diabetes with Hba1c 6.2 on gliclazide, metformin and sitagliptin. On admission her Glucosewas 449 mg/dl, pH 7.11, pCO2 11 mm.Hg, HCO3 4.4 mmol/l, aniongap 21, urine ketones 4+.Alpelisib was stopped and patient was treated in the ICU with insulin infusion , IV fluids and DKA resolved in 34 hr. She was discharged after 5 days with gliclazide, metformin and glargine and asked to continue monitoring her glucose levels. She was initiated on bilastine for the rash.

Two week post discharge she visited her oncologist and was restarted on Alpelisib 250mg. At time of reintiation her sugars were in the range 120-170 and her glargine has been discontinued due to hypoglycaemic episodes. 2 days after reinitiation of Alpelisib she presented to emergency with emesis and rash. Her rbs was 398, pH 7.21, pCO2 18mm.Hg, HCO3 11.4 mmol/l, aniongap 21, urine ketones 2+. Her Alpelisib and gliclazide was again discontinued and patient was initiated on iv insulin which was transitioned to s/c insulin next morning . On day 5 of admission her insulin was stopped due to low blood glucose readings and she was discharged on gliclazide, metformin and sitagliptin .

After combined decision with oncologist and patient, it was decided not to reinititate her Alpelisib. Her HbA1c was 6.4 % on follow after 3 months.

Case 4

81 yr old patient of breast cancer for past 17 yr presented to orthopedics department with back pain and was diagnosed to have metastasis to the vertebrae. She was on metformin, vildagliptin and dapagliflozin with a Hba1c of 7.3. She was found to have a PIK3CA gene mutation and was initiated on Alpelisib and was advised to monitor her blood glucose levels. After 2 months she was brought to the emergency with 2 days history of nausea and vomiting and unconsciousness since past 3 hrs. At admission she was observed to be dyspneic with ketone breath. Her blood glucose was 612 mg/dl. The laboratory data revealed pH 7.01, pCO2 7.8mmHg, HCO3 4.9 mmol/l, anion gap 19, urine ketones + 4, hba1c of 10.6(rise of 2.3 % since 2 months) and sodium of 119 nmol/l (after correction for hyperglycaemia). She was successfully treated with fluids and insulin intravenously and electrolyte correction. She OAD and Alpelisib were discontinued and she discharged after 12 days on metformin, linagliptin and pioglitazone.

10 days after discharge. oncology made a decision to restarted Alpelisib at a dose of 250mg with monitoring of blood glucose. This patient developed mild hyperglycaemia with blood sugars upto 250 mg. Given her advanced age and apprehension to insulin, Patient was put on continuous glucose monitoring. At 3 months follow up her hba1c was 7.9 %.

Case 5

61 yr old female known case of breast cancer was initiated on Alpelisib .Her initial HbA1c was 7.1% on metformin. 3 weeks after starting alpelisib, she presented with multiple episodes of nausea and vomiting. her glucose was 360 mg/dl. The laboratory data revealed: pH 7.26, pCO2 18mm.Hg, HCO3 12.7 mmol/l, aniongap 22, urine ketones 3+. The patient was diagnosed with DKA and admitted in the ICU with the initiation of appropriate treatment including intravenous fluids, insulin and electrolyte replacement.

She was diagnosed with DKA, successfully treated with fluids and insulin. Metformin was stoppedalong

with Alpelisib. On subsequent revisit she was started with pioglitazone and dapagliflozin alongwith reintroduction of Alpelisib at 250 mg by the oncologist. 3 months followup her hba1c was 7.5 %.

Discussion

With this observational study we wish to highlight and analyse the phenomenon of severe lifethreatening hyperglycaemia that can be associated with Alpelisib use in patient of breast cancer. Any patient on Alpelisib presenting to the emergency should be screened for hyperglycaemia. While Alpelisib associated ketoacidosis remains a rare entity , there are several points to be discussed from the view of clinical picture and management .Patients on Alpelisib presenting with DKA have similar symptoms to those not on Alpelisib, however it may occur more rapidly . Patients usually present with nausea, vomiting, pain abdomen, malaise, polydipsia, polyphagia, tachypnea and signs of dehydration. In our patients vomiting, nausea and pain abdomen were major symptoms Other symptoms such as increased thirst, tachypnea and weakness were also observed. In patients with metastatic breast cancer, weakness, nausea and vomiting may be associated with side effects of chemotherapy and disease burden also. Thus it is important to remain vigilant regarding these symptoms. Diabetic ketoacidosis may present in those without diabetes as observed in the first patient and has been observed previously also in other case reports.(8)

In our study, one patient was non diabetic while 4 patients had history of type 2 diabetes but all were good to moderate control with a highest HbA1c of 7.9. All patients were postmenopausal with minimum age of 48 yr and maximum age of 81 yr. Median duration of breast cancer diagnosis was8 yr with a range of 6-17 yr Hyperglycaemia and DKA improved within 3 days for all patient with control of hyperglycaemia which similar to what was seen in SOLAR 1 trial (4).

All of the patients in the study had metastatic breast cancer with PIK3CA mutation and were put on 300mg of Alpelisib. Timing of DKA post initiation of Alpelisib varied from 7 days to 62 days, median duration of 17 days. SOLAR 1 trial also demonstrated a median duration of 15 days for onset of hyperglycaemia post Alpelisib initiation with a range of onset from 5-395 days.(9). A large database of Adverse effects of Alpelisib also observed that most sideeffects occurred within 30 days of drug initiation.(10) Only one patient had recurrent DKAafter reinitiation of Alpelisib following which it had to be discontinued . However , the second episode occurred within 48 hr of reinitiation . This is similar to what has been seen with other cases also where blood glucose increased rapidly after reinitiation but returned to baseline in a few days after Alpelisib was discontinued (8,11,12,13) . The explanation for the same is not known ,however it has been theorised that worsening of hepatic and peripheral insulin resistance causing heightened insulin resistance with increased dependency on PI3K/AKT/mTOR pathway . When Alpelisib is reintroduced it interferes with PI3K/AKT/mTOR pathway leading the immediate hyperglycaemia (13). This theory has gained evidence following demonstration on Continous glucose monitoring(CGM) showing severe and persistent hyperglycaemia consistent with pharmacodynamics of the drug (14)

Safety of Alpelisib has not been established in Type 1 diabetes and uncontrolled type 2 diabetes as trials excluded these patients. Only 56 % patients in SOLAR 1 had prediabetes and only 4 % had diabetes. Even amongst these 63.7 % reported hyperglycameia with 0.4% patients developing DKA with 6 % requiring discontinuation due to hyperglycaemia(3). Severe hyperglycaemia including DKA with fatal outcomes has also been observed (15).

While most of insulin's effects initiate through the activation of the phosphatidylinositol-3-kinase (PI3K)/AKT signaling pathway, which is essential for facilitating glucose transport, particularly by enhancing glucose uptake and glycogen storage in the liver and skeletal muscles. This pathway is activated when insulin binds to its receptor, leading to kinase activity that phosphorylates the receptor, thereby activating PI3Ksubsequently activating AKT, leading the GLUT4 glucose transporter to move to the plasma membrane .Any disruption in the PI3K/AKT pathway can result in insulin resistance and hyperglycemia.(5)

The PI3K inhibitor alpelisib disrupts this pathway, preventing glucose uptake in skeletal muscle and adipose tissue while enhancing hepatic gluconeogenesis (5). Individuals with a history of diabetes may need more intensive treatment, and glucose monitoring is critical, particularly for those with diabetes or prediabetes. Continuous glucose monitoring (CGM) offers a non-invasive approach to closely track glycemic trends, allowing for timely intervention to prevent metabolic deterioration (14). Delayed management could compromise metabolic control, necessitating adjustments to or discontinuation of alpelisib. Though the impact of alpelisib-induced hyperglycemia on survival rates is not yet clear, higher doses of Alpelisib correlate with extended time to disease progression. Reduction in dose andInterruptions in alpelisib therapy reduce its efficacy, potentially depriving patients of a treatment that improves both quality of life and survival.

Multiple management strategies have been proposed in Consensus guidelines and well as other studies (16,17,18,19,20). In SOLAR 1 trial OAD were effective in managing hyper glycaemia however 28% needed 3 or more OAD (4). Discontinuation of Alpelisib is needed for management of grade 3/4 hyperglycaemia including DKA with dose reduction of Alpelisibbeing a final option if glycaemic targets are not met (21) but grade1 /2 hyperglycaemia can usually be managed without adjusting alpelisibdose.

Metformin and other insulin sensitisers such as pioglitazone have been widely accepted for hyperglycaemia associated with Alpelisib use. Recent studies have also shown SGLT2 I to also be effective (22). Mainstay of management include initial Hba1c < 8% , ensuring regular blood glucose monitoring , early detection of hyperglycaemia and timely referral to endocrinologist.

Conclusion

Here we reports 5 cases of DKA associated with Alpelisib use highlighting the need for glycaemic monitoring while initiating . Though Hyperglycaemia is a common side effect of Alpelisib therapy, it has also been proposed that hyperinsulinaemism associated with hyperglycaemia can reduce its efficacy. A perfect balance between dosage, treatment duration, and hyperglycemia management provides the best chance of maximising the clinical benefits of this drug. A detailed evaluation of preinitiation factors such as good glycamic control should be considered in such patients. Given the high incidence of hyperglycaemia in patients reinitiated on Alpelisib after DKA, we propose that such patients be considered for hospital admission when restarting Alpelisib is being considered.

Declarations

Funding

This research received no external funding.

Conflicts of interest

The authors declare no competing interests.

Data availability

All data generated or analyzed during this study are included in this published article.

Ethical approval

The approval of the ethics committee was obtained before the initiation of the study . Ethics statement has been added to the manuscz

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